

absence of neurologic changes is of importance in determining whether or not heart failure will occur, the fundamental mechanism of the heart failure must be explained in another way, since muscular exercise does not cause a normal heart to fail. A number of hypotheses have been put forth to explain this mechanism, and they may be reviewed briefly.

MECHANISM OF HEART FAILURE

Any explanation of the mechanism of heart failure in beriberi must account for two outstanding features: first, the predominance of cardiac enlargement on the right side, and second, the disturbed contractility.

The various hypotheses which attempt to explain these abnormalities may be summarized as follows:

The Vagus Hypothesis.—One of the oldest hypotheses as to the cause of heart failure in beriberi is that it is due to degeneration of the vagus nerves. This hypothesis was proposed when less exact information was had regarding the functions of the vagus. One may say, at present, that there is no evidence that paralysis of the vagus can cause the picture of heart failure seen in beriberi. This is supported by the fact that many patients have heart failure without any evidence of vagal involvement, and when tachycardia develops as a result of paralysis of the vagus with atropine, the heart decreases rather than increases in size.¹⁴ It would seem unlikely, therefore, that vagal paralysis is responsible for either the heart failure or the cardiac enlargement in these patients. This opinion has also been expressed by Stanley,¹⁵ Aalsmeer and Wenkebach, Shimazono and others.

Hypothesis of Respiratory Paralysis.—The hypothesis that heart failure in beriberi results from respiratory paralysis was first proposed by M. Muira.¹⁸ He felt that the hypertrophy of the right side of the heart was due to a retraction of the lungs and to an elevation of the diaphragm and a contraction of the branches of the pulmonary arteries. However, Matsuoka¹⁹ did not find changes in the pulmonary vessels in fatal cases of beriberi. He felt that the dilatation and hypertrophy of the right side of the heart were probably due to the collapse and congestion of the lung that follows hydrothorax, and to the high position of the diaphragm. This explanation fails to account for the presence of heart failure with enlargement of the right side of the heart in the absence of hydrothorax or diaphragmatic paralysis.

The Water Retention or Edema Hypothesis.—The hypothesis that heart failure in beriberi is due to retention of water was recently pro-

18. Muira, M.: Nachtrage zur Pathologie der Kakke, Virchows Arch. f. path. Anat. **117**:159, 1889.

19. Matsuoka, Y.: On the Pathological Anatomy of the Lungs in Beriberi (Kakke), J. Path. & Bact. **20**:191, 1915.

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Whereas the histology of the light parts of the cortex was fairly uniform, that of the dark parts was more irregular. Here the interstitial tissue was frequently increased in amount and contained increased collagenous connective tissue. One saw occurring infiltrations of small, round cells which in part adjoined hyalinized glomeruli (fig. 5). In other places, the interstitial tissue was swollen and contained polymorphonuclear leukocytes, many of which were seen entering the tubules. Everywhere in the interstitial tissue of the dark parts of the cortex one often found large, xanthoma-like cells (fig. 6), which were stained yellowish by sudan and which were doubly refractile. The tubules of the scarred parts

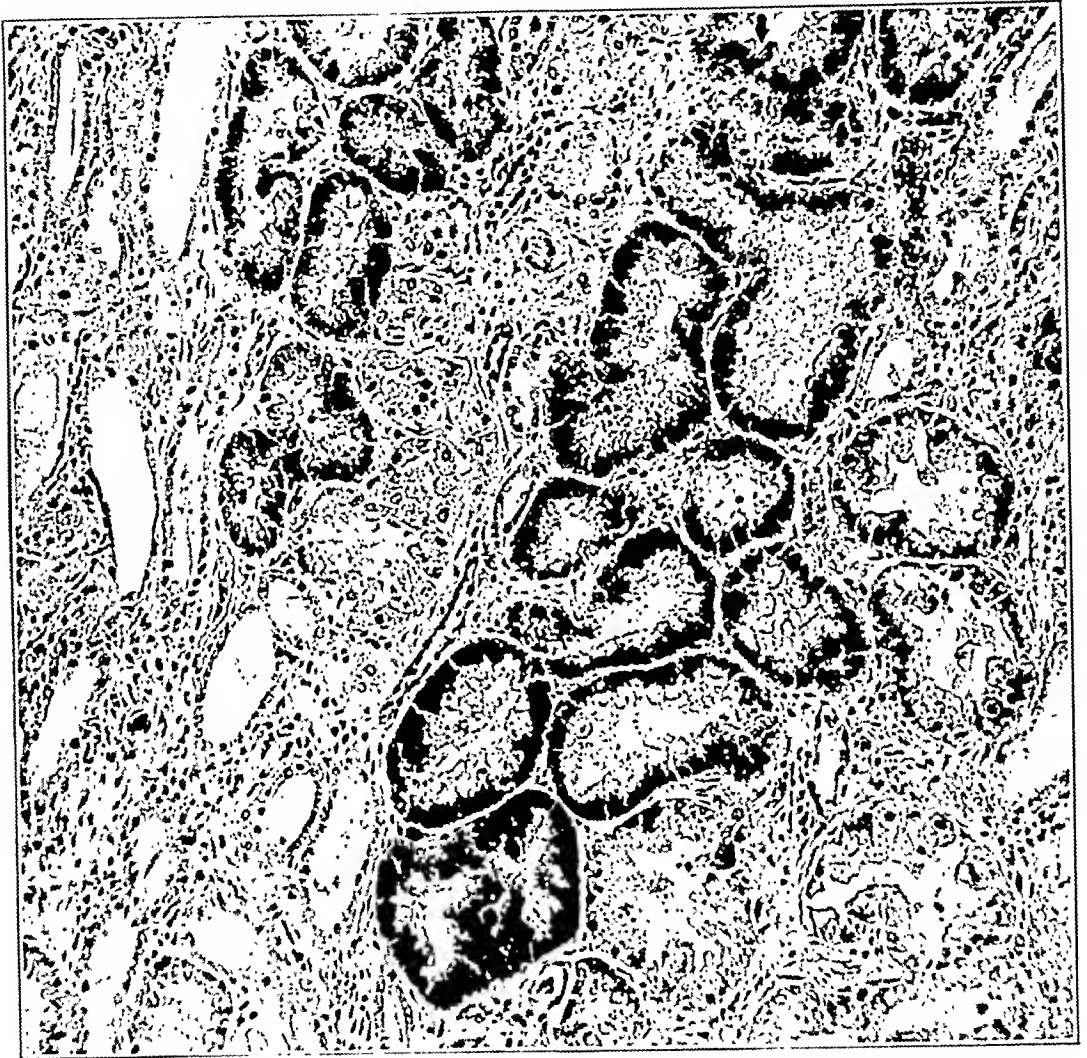


Fig. 4.—Extensive hyaline droplet-like degeneration of major pieces. Gram stain; $\times 160$.

were in all stages of atrophy and degeneration up to entire disappearance. Their epithelial cells were not, or only very little, enlarged, and were much more desquamated than those of the light part of the cortex. Many of them contained a large amount of fat, which was irregularly arranged. Occasionally one saw signs of regeneration. In some places one found calcified casts.

The number of glomeruli appeared to be much decreased, but this decrease seemed to be only relative, caused mainly by the enlargement of the kidneys. Most of the glomeruli were located in the dark parts of the cortex. Fifty per cent of the glomeruli—500 were differentiated—were well preserved (fig. 6), some being

effect on the symptoms although there may be an increase in the reducing power of the blood. Sodium lactate, glycerin and alkalis have no effect on the symptoms.

The experiments of Mann and Magath and of Noble and Macleod are similar, and in the main the results coincide. Taking these observations into consideration, we may conclude that dextrose, the only sugar which can definitely counteract the symptoms that accompany the hypoglycemia due either to insulin or to the removal of the liver, shows a definite depressive action on the secretions of the gastric, pancreatic and biliary glands. Maltose, levulose and galactose may slowly or inconspicuously cause the same action. Sucrose and lactose have no apparent effect on the secretory activity of the digestive glands. From the foregoing fact it is evident that the available sugar that has an inhibitory influence on the secretory center of the digestive juices must be ready or easily changeable to be ready for use in the physiologic process of oxidation.

The importance of the autonomic nervous centrum and the vagus for the excitatory as well as the inhibitory impulses in the process of humoroneural regulation is further demonstrated in dogs by severing both vagi directly above the diaphragm. Four dogs provided with gastric fistulas showed, in hypoglycemia caused by insulin, a distinct stimulation of the gastric secretion, and in hyperglycemia caused by the injection of dextrose, a marked inhibition of secretion; while none of those in which both vagi were severed (four experiments in three dogs) showed an increase of secretion in hypoglycemia or a distinct decrease of secretion due to the injection of dextrose. The same fact was also proved by one of us (K. K.) in experiments on the pancreatic and biliary secretions of dogs. In these researches it might be especially emphasized that the dose of insulin and the degree of hypoglycemia must be sufficient to cause a distinct reaction; otherwise, even the contrary result may be obtained although the vagi are intact. This phenomenon is perhaps due to the fact that the secretory mechanism is rather inhibited by insulin directly, and therefore a strong excitatory hypoglycemic influence is necessary to provoke the reaction.

It is well known that protein, if introduced into the digestive tracts, has directly no excitatory effect on the secretory activity of the digestive juices, while its digestive products are believed to excite the gastric secretion. It is further known that these products, if introduced from a fistula into the stomach isolated from the pyloric portion and the intestine, do not cause any secretion. It is evident, therefore, that these products cause, chemically, no excitatory influence on the secretory activity of the mucous membrane of the stomach. It is desirable further to make clear the mechanism of this excitatory function. We

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The amino-acids that were used for our investigation, invariably caused a pronounced secretion of the gastric juice when administered intravenously or intraduodenally to man and to dogs. This secretion

TABLE 18.—Results of the Analyses of the Contents of the Stomach Following an Intravenous Injection of 100 Cc. of a 5 per Cent Solution of Glycocoll in a Dog with Both Vagi Severed Directly Above the Diaphragm and Provided with a Gastric Fistula

Dog 4, a female, weighing 15.4 Kg.; experiment twenty-nine days after severing the vagi and six days after providing a gastric fistula

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	71	101	8.6
1/2.....	0.078	65	97	7.0
3/4.....	66	97	4.2
1.....	0.080	69	104	4.2
Following an injection of glycocoll				
1/4.....	0.110	70	104	2.4
1/2.....	0.103	70	104	5.5
3/4.....	0.096	67	100	4.0
1.....	0.092	53	87	2.8
1 1/4.....	0.089	53	90	2.8
1 1/2.....	0.082	54	89	2.8
1 3/4.....	0.082	54	88	2.0
2.....	0.085	47	86	1.3

TABLE 19.—Results of the Analyses of the Contents of the Stomach Following an Intravenous Injection of 100 Cc. of 2.31 per Cent (Mol/10) Glutamic Acid Hydrochloride

A. Dog 5, female, weighing 15.0 Kg.; experiment done twenty-two days after providing a gastric fistula				B. Dog 4, female, weighing 15.4 Kg.; experiment done eighty-nine days after severing both vagi, and sixty-six days after providing a gastric fistula			
Times at Which Specimens Were Collected, Hours	Gastric Juice			Times at Which Specimens Were Collected, Hours	Gastric Juice		
	Free Hydrochloric Acid	Total Acidity	Amount of Juice, Cc.		Free Hydrochloric Acid	Total Acidity	Amount of Juice, Cc.
Fasting				Fasting			
1/4.....	85	103	9.0	1/4.....	48	75	1.0
1/2.....	110	126	6.8	1/2.....	72	93	0.6
3/4.....	112	125	10.4	3/4.....	73	93	0.8
1.....	104	117	8.0	1.....	72	93	0.5
Following an injection of glutamic acid hydrochloride				Following an injection of glutamic acid hydrochloride			
1/4.....	62	74	4.0	1/4.....	About the same acidity as before the injection		0.3
1/2.....	94	104	1.0	1/2.....			0.2
3/4.....	93	112	1.2	3/4.....			0.2
1.....	103	113	6.6	1.....			0.2
1 1/4.....	112	122	15.6	1 1/4.....	72	93	0.2
1 1/2.....	114	121	13.0	1 1/2.....			1.5
1 3/4.....	118	126	11.0				
2.....	116	125	2.0				

was inhibited by an injection of dextrose or atropine sulphate. In a dog in which both vagi were severed directly above the diaphragm, this excitatory influence was not shown. From these facts it is evident that

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Our experiment showed also that fats are strong excitants of pancreatic and biliary secretions. The characteristic feature of the juice secreted in the stimulation of fats is that it is extraordinarily thick and rich in pancreatic ferments, bile pigments and bile acids. This property is pronounced and characteristic, regardless of whether fats are introduced intraduodenally or intravenously. This secretion is distinctly inhibited by the injection of dextrose or atropine, so that it is evident that fats stimulate the autonomic nervous centrum and from this centrum the stimulus is transmitted through the autonomic nervous system to the

TABLE 24.—*Results of the Analyses of the Contents of the Duodenum Following the Intraduodenal Injection of Olive Oil in the Amount of 1 Gm. per Kilogram of Body Weight in a Man with Diabetes Mellitus, Aged 21, Weighing 52 Kg.*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Duodenal Return					
		Amount of Juice, Cc.	Trypsin Units (Amount \times Activity)	Amylase Units (Amount \times Activity)	Lipase Units (Amount \times Activity)	Bile Pigment (Dilution \times Amount)	Bile Acids (Dilution \times Amount)
Fasting							
$\frac{1}{4}$							
$\frac{1}{2}$	0.124	27.5	5,500	68,145	27,500	605	8,250
$\frac{3}{4}$							
1	0.110	18.0	9,000	57,600	46,800	1,008	9,900
Following an injection of olive oil							
$\frac{1}{4}$	0.112						
$\frac{1}{2}$	0.123	9.6	4,800	25,709	38,880	864	12,480
$\frac{3}{4}$	0.122						
1	0.118	34.0	17,600	92,106	188,700	8,160	255,000
$1\frac{1}{4}$	0.123						
$1\frac{1}{2}$	0.122	40.5	20,250	100,359	91,125	6,075	182,250
$1\frac{3}{4}$	0.119						
2	0.116	35.0	11,200	84,000	89,250	2,310	28,000
$2\frac{1}{4}$	0.117						
$2\frac{1}{2}$	0.120	23.2	4,640	63,545	46,400	812	10,440
$2\frac{3}{4}$	0.122						
3	0.123	22.2	4,440	63,714	23,860	555	7,770
$3\frac{1}{4}$	0.122						
$3\frac{1}{2}$	0.124	9.0	900	27,414	17,100	324	4,050
$3\frac{3}{4}$	0.127						
4	34.5	11,040	98,981	23,460	207	1,725

reacting tissue cells. The action of fats on the gastric secretion is, in our experiments, dualistic; i. e., it is sometimes inhibitory and at other times excitatory.

It is now apparent that dextrose causes an inhibitory stimulation of the autonomic nervous center, and amino-acids and fats on the contrary an excitatory stimulation. Amino-acids act electively on the center that controls the gastric secretion, while fats act on the centrum that controls pancreatic and biliary secretions, though that of gastric secretion is not quite excluded. From these facts it seems interesting to investigate whether dextrose has a decisive inhibitory influence on the gastric secretion, and in consequence on the secretin mechanism, when a usual mixed diet is administered. For this purpose we introduced a certain

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quantity of dextrose solution into the duodenum, and at the time when its inhibitory action was evident (usually thirty minutes afterward), the test breakfast, meat extract, rice-bran extract, alcohol and caffeine solutions, all of which are known as marked excitants of the gastric secretion and are widely used to determine the secretory activity of the stomach, were given by mouth. As the controlling experiment we introduced into the duodenum the same amount of distilled water as of dextrose solution, and compared the results of both procedures on the

TABLE 27.—*Results of the Analyses of the Gastric Juice of a Man, Aged 23; A, Following the Intraduodenal Injection of 200 Cc. of a 25 per Cent Solution of Dextrose and the Administration by Mouth of 200 Cc. of Rice-Bran Extract; B, Following the Intraduodenal Injection of 200 Cc. of Distilled Water, and the Administration by Mouth of 200 Cc. of Rice-Bran Extract**

A			B		
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice: Free Hydrochloric Acid	Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice: Free Hydrochloric Acid
Fasting			Fasting		
$\frac{1}{4}$	65	$\frac{1}{4}$	42
$\frac{1}{2}$	0.113	74	$\frac{1}{2}$	36
$\frac{3}{4}$	57	$\frac{3}{4}$	14
1	0.101	45	1	0.089	10
Following an injection of dextrose			Following an injection of distilled water		
$\frac{1}{4}$	0.160	26	$\frac{1}{4}$	0.093	0
$\frac{1}{2}$	0.207	29	$\frac{1}{2}$	0.100	4
Following the administration of rice-bran extract			Following the administration of rice-bran extract		
$\frac{1}{4}$	0.161	0	$\frac{1}{4}$	0.096	0
$\frac{1}{2}$	0.122	0	$\frac{1}{2}$	0.089	0
$\frac{3}{4}$	0.083	0	$\frac{3}{4}$	0.075	0
1	0.062	0	1	0.087	20
$1\frac{1}{4}$	0.074	0	$1\frac{1}{4}$	0.094	43
$1\frac{1}{2}$	0.072	20	$1\frac{1}{2}$	0.103	38
$1\frac{3}{4}$	0.072	46	$1\frac{3}{4}$	0.103	18
2	0.089	64	2	0.101	20
$2\frac{1}{4}$	0.083	56	$2\frac{1}{4}$	0.096	22
$2\frac{1}{2}$	0.081	62	$2\frac{1}{2}$	0.098	7
$2\frac{3}{4}$	0.083	55	$2\frac{3}{4}$	0.101	25
3	0.080	43	3	0.098	73

* The acidity of the gastric juice after the injection of dextrose is not low but the amount of juice to be collected was reduced to the minimum, so that the inhibitory action of dextrose was evident. The appearance of free hydrochloric acid after administration of rice-bran extract was about thirty minutes later than in the control research, and the disappearance of the rice-bran remnants from the stomach was also about thirty minutes slower.

gastric secretion. The result of the test breakfast was shown in the fourth paper of the present series.

These observations proved that dextrose inhibits the stimulating effect of all ingested excitants of the gastric secretion. After an injection of dextrose, the reappearance of the free hydrochloric acid when the substances mentioned were ingested was postponed from thirty minutes to one hour and fifteen minutes in comparison with control researches. The reappearance of the free hydrochloric acid in the latter depended on the test substances used; it occurred latest when

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suppressed and no secretion occur although appetizing foods are ingested. In hypoglycemia the autonomic nervous center is stimulated humoroneurally; therefore, if foods are ingested at this time, the neural excitation is added to the stimulation and the secretion is especially abundant. The hypoglycemia alone also causes humoroneurally an abundant secretion of the gastric juice, but if a sudden inhibitory neural impulse occurs, such as fright, anger, disappointment, pain, etc., this secretion might be entirely suppressed. From the foregoing facts it is evident that the neural and the humoroneural mechanisms cooperate sometimes while at other times they inhibit each other. In the second phase of the gastric secretion, the humoroneural excitants play a rôle to some extent.

A purely humoral mechanism of the gastric secretion must also exist. It is well known that histamine provokes humorally the gastric secretion. We observed that hyperglycemia or atropine does not inhibit the secretory activity caused by histamine. It was also proved in our experiment that the severing of both vagi has not much influence on the excitatory activity of histamine.

It might be emphasized also that hypoglycemia and hyperglycemia act on the motility and sensation (hunger and satiation) of the digestive tracts in the same way as on the secretion.

The secretions of pancreatic juice and bile are controlled by the three mechanisms mentioned. The neural mechanism seems to play a lesser rôle in these glands than in the salivary and gastric glands. When acid chyme is poured from the stomach into the duodenum, the secretin mechanism develops at once, and there is active humoral secretion of pancreatic juice and bile. When the humoroneural excitants, like fats, are resorbed there is also marked secretion through this mechanism. We observed many substances which cause neurally (reflex) abundant secretions of pancreatic juice and bile when injected intraduodenally; this is not the normal reaction, however, as the reflex secretions usually failed or were scant when these substances were ingested by mouth. On the other hand, some inadequate irritation of the duodenal mucous membrane, for example, application of concentrated saline solution or some dye stuffs for clinical purposes, causes nausea and vomiting or diarrhea; even when these symptoms fail, a reflex inhibitory impulse develops which stops the secretions caused neurally or humoroneurally. Hyperglycemia and hypoglycemia humoroneurally inhibit and excite these secretions and the relation between this activity and the neural mechanism is the same as in gastric secretion.

The secretion of pancreatic juice and bile is undisturbed even when gastric secretion fails entirely, as in achylia gastrica or in cancer of the stomach. In these cases, the secretory activity progresses mainly humoroneurally in association with the neural mechanism.

THE BERIBERI HEART*

CHESTER S. KEEFER, M.D.

PEIPING, CHINA

One of the outstanding characteristics of many patients with beriberi is cardiac insufficiency. This type of cardiac insufficiency is caused by changes in the cardiovascular system which are dependent on a deficient diet. The deficiency has been shown to be due to a lack of vitamin B. In this paper, I wish to present the results of a study of two groups of patients with beriberi, directing special attention to the cardiovascular system. I shall emphasize and discuss certain differences that are present.

In the first group of fifteen patients, cardiac insufficiency was demonstrated, and in the second group of twelve patients no obvious symptoms of cardiac insufficiency were observed.

PATHOLOGIC CHANGES IN BERIBERI

The papers of Pekelharing and Winkler,¹ Nocht,² Muira,³ Vedder,⁴ Kasuma,⁵ Herzog⁶ and Scheube⁷ may be consulted for a detailed description of the pathologic changes occurring in beriberi. For the purpose of this paper, the main pathologic changes may be grouped as follows: (1) degeneration of the peripheral nerves, including both the motor and the sensory elements; (2) edema of the subcutaneous tissues and muscles, and effusion of fluid into the serous cavities and (3) dilatation of the heart, particularly of the right side, with fatty infiltration and a moderate degeneration of the myocardium.

These changes lead to peripheral neuritis, edema of the tissues and signs of cardiac insufficiency. In many patients, one or the other group

* Submitted for publication, July 9, 1929.

* From the Department of Medicine of the Peiping Union Medical College.

1. Pekelharing, C. A., and Winkler, C.: *Mitteilungen über die Beriberi*. Deutsche med. Wchnschr. **39**:845, 1887.

2. Nocht, B.: *Beriberi Menses: Handbuch der Tropischen Krankheit*, Leipzig, Johann Ambrosius Barth, 1924, vol. 2, p. 450.

3. Muira, K.: *Beriberi oder Kakke*, *Ergebn. d. inn. Med. u. Kinderh.* **4**:280, 1909.

4. Vedder, E. B.: *Beriberi*, New York, William Wood & Company, 1913.

5. Kasuma: *Ueber die veränderungen des Herzens und Gefäss System bei Kakke (Beriberi)*, Third Congress, Saigon, 1913, *Far Eastern A. Trop. Med.* **3**:383, 1914.

6. Herzog, M.: *Studies in Beriberi*, *Philippine J. Sc.* **1**:709, 1906.

7. Scheube: *Die Beriberi Krankheit*, Jena, Gustav Fischer, 1894.

REPORT OF CASE

History.—N. H., aged 75, a wheelwright, was admitted to the Johns Hopkins Hospital medical service, on Feb. 8, 1929, and was discharged on March 8, 1929. One brother had a "weak" heart, but there was no other history of cardiac disease in the family. The patient had enjoyed excellent health prior to the onset of his present illness. He had not been confined to bed by illness for fifty years. At the age of 25 he had suffered for ten days with swollen, painful ankles and fever. He knew of no heart complications associated with this illness. There had been no recurrences of "rheumatism," and he had never had chorea. He had been singularly free from head colds and sore throats. A Neisserian infection at the age of 35 had left no symptoms, and syphilis was denied by name and by its common stigmas.

The patient had performed hard labor until twelve years before entry to the hospital, without any symptoms related to the cardiovascular system. At this time he abandoned his occupation as a wheelwright, not because of ill health but because he considered he had attained an age justifying retirement. For the past twelve years he had no regular occupation but performed infrequent odd jobs not involving any severe physical test.

Seven years before entry, he was seen in the outpatient department of the Johns Hopkins Hospital for relief from constipation. Examination of the heart at that time revealed no enlargement to the right; dulness to the left 11 cm. in the fifth space. Rhythm was regular; sounds were clear and there were no murmurs. The blood pressure at that time was 134 systolic and 80 diastolic. Five weeks before entry the patient caught "cold in his chest," had a slight nonproductive cough and a dull pain in the left side of the chest, which was not exaggerated by breathing but which was made worse by exercise. This pain did not radiate to the shoulder or down either arm and was associated with neither breathlessness nor anxiety.

After a week's rest in bed at home, the patient came to the outpatient department again. During his entire life he had never suffered from dyspnea, orthopnea or edema of the ankles. On examination the physical observations were essentially the same as those noted subsequently. Because of an unusual type of cardiac arrhythmia demonstrated by electrocardiographic examination, further studies were advised, and he was sent home until arrangements for admission to the ward could be completed.

Physical Examination.—The temperature was 99 F. (R); the pulse rate, 75; the apex rate, 77, and respirations, 20. The blood pressure was 235 systolic and 110 diastolic. The height was 5 feet 4½ inches and the weight was 156 pounds (70.8 Kg.). The patient appeared to be well developed, well nourished and intelligent; he looked much younger than his stated age. There was no orthopnea, dyspnea, edema or cough, but slight cyanosis of the lips and nail beds was present. The skeletal system was normal save for slight hypertrophic arthritis of the small joints of the hands.

The pupils were equal and central with quick reaction to light and on accommodation. There was moderate arcus senilis. Extra-ocular movements were normal.

The media and disks were clear. The retinal arteries were moderately tortuous and smaller than normal. No exudates or hemorrhages were noted.

The mouth, nose and ears were normal save for complete adentia.

There was no enlargement of the lymph nodes.

The trachea was in the midline; no tugging was observed. The thyroid gland was not enlarged. There was moderate engorgement of the cervical veins with regular and normal pulsations occasionally interrupted by from eight to ten irregular and more rapid waves.

of symptoms predominates, and in order to emphasize this fact the following classification has been used by many: (1) neuritic type, (2) edematous type, (3) mixed type and (4) cardiac type.

PATIENTS WITH CARDIAC INSUFFICIENCY

In this group there were fifteen patients. Their main complaints were typical of those suffering from cardiac insufficiency. Thirteen survived and two died. One of the patients who died had extensive pulmonary tuberculosis; the other had diaphragmatic and intercostal paralysis with bronchopneumonia. Both of these patients had cardiac enlargement, tachycardia and signs of congestive heart failure.

Symptoms and Signs of Cardiac Insufficiency.—All the patients complained of excessive fatigue and palpitation on exertion. Shortness of breath was felt, but it was not so pronounced as the first two symptoms. Edema of the lower extremities was present in every case, and in many it was the first sign of the disease. One must be cautious in attributing edema to a failing heart under such conditions, since it is frequently a symptom without any other supporting evidence of heart failure. In these patients, the edema was never considered to be the result of cardiac insufficiency unless there were other unequivocal signs. Four of the patients had enlarged livers. Ascites was present in one, and hydrothorax could be demonstrated in four. There were signs of pulmonary congestion in only three patients.

Examination of the heart revealed a cardiac rate that varied from 52 to 136 beats per minute, the average being 106. The rhythm was normal. The heart rate was labile, the slightest exertion causing a great increase. There was engorgement of the cervical veins with increased pulsation in four patients. Increased arterial pulsation with a collapsing pulse, capillary pulsation and increased arterial sounds over the brachial and femoral vessels were present in five patients.

The cardiac impulse was usually feeble and diffuse. A systolic thrill was felt over the apex in four patients, and in two patients a palpable thrill could be felt over the carotid vessels in the neck.

The cardiac dulness was increased in every case. The increase occurred both to the right and to the left of the midsternal line, and in the second and third left intercostal spaces. Associated with the cardiac enlargement there were systolic murmurs at the apex and over the pulmonary area in ten cases. The pulmonary second sound was accentuated in ten of the patients. There were no diastolic murmurs.

Neurologic Symptoms and Signs.—The changes in the nervous system were comparatively mild. The most severe changes were noted in the two patients who died. In one of these there was a motor and sensory paralysis of both legs, and in the other there was diaphragmatic

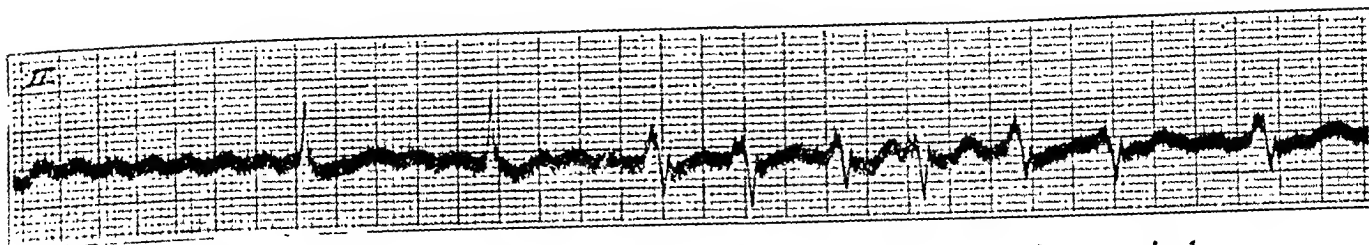


Fig. 3.—Record taken Feb. 9, 1929. Lead II shows transition from auricular fibrillation with very slow rate and normal intraventricular conduction to a more rapid rate with auricular fibrillation and delayed intraventricular conduction.

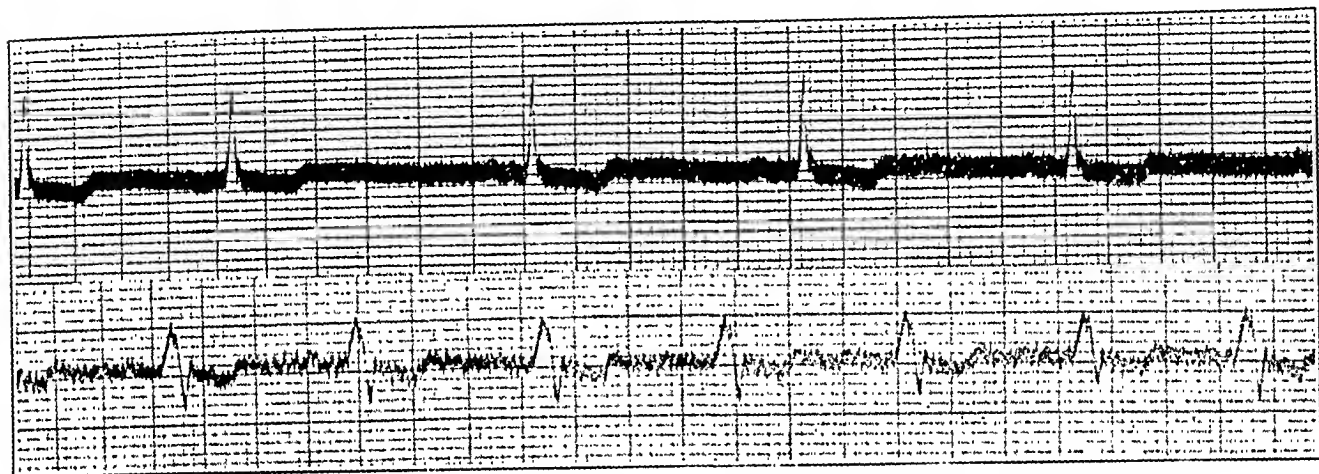


Fig. 4.—Record taken Feb. 13, 1929. The upper curve shows normal sinus rhythm with normal intraventricular conduction. The rate was 58; P-R interval, 0.17 seconds. The lower curve was taken five minutes later. The cardiac rate was increased by exercise of the right leg with electrodes in place. The rate was 91; P-R interval, 0.16 seconds; QRS, 0.12 seconds. There was normal sinus rhythm and delayed intraventricular conduction.

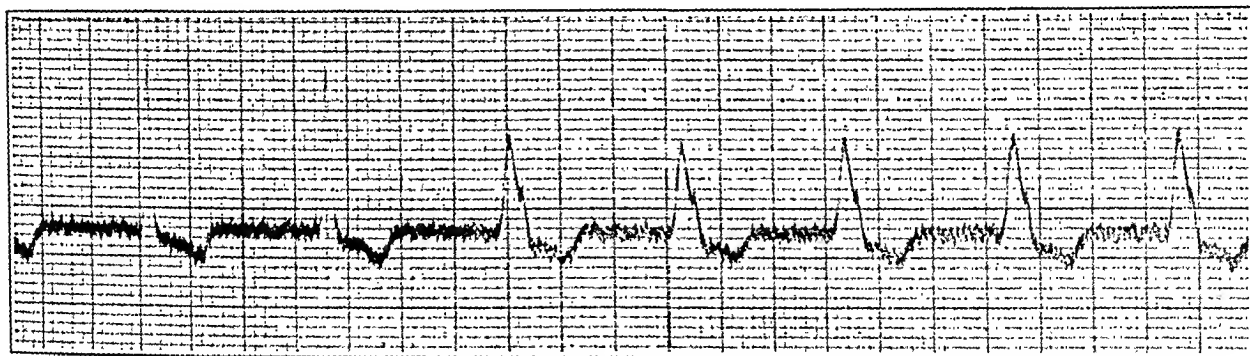


Fig. 5.—Record taken Feb. 13, 1929—Lead I: Same experiment as shown in figure 4 but actually showing the transition from normal sinus rhythm with normal intraventricular conduction to normal sinus rhythm with delayed intraventricular conduction with faster rate induced by exercise of the extremity free from electrodes.

and intercostal paralysis. In all the other patients, the neuritis was mild and varied in degree. The knee and ankle jerks were absent, but the muscular power was good, except in the two patients who died.

The sensory disturbances were mild, and when they occurred they consisted of a diminution of touch and vibratory sense. The sensation of touch was diminished over a greater area than were the other sensations, and this feature was much more marked in the presence of edema.

The striking feature in these cases was the comparative lack of extensive neurologic changes, and the preservation of muscular power. This is of considerable importance, since the patients who have the most marked changes in the central nervous system, have the least changes in the cardiovascular system. This point will later be discussed in greater detail.

Blood Pressure.—There were no constant changes in the blood pressure. It was either normal, increased or decreased. The systolic pressure varied from 82 to 150 and the diastolic from 35 to 100 millimeters of mercury. The pulse pressure averaged 45. If the blood pressure was high during the acute stage of the illness, it gradually became normal during convalescence. The systolic pressure usually fell before the diastolic pressure became normal. In some, the systolic pressure fell as the diastolic increased, and in others, both pressures increased simultaneously. Although an increased pulse pressure was not a constant feature in these cases, it was not an uncommon observation. It was obvious, however, that the patients with the highest pulse pressures were the ones with the most marked peripheral vascular changes. There was no correlation between the size of the heart and the changes in the blood pressure.

These observations are in agreement with those of previous investigators, such as Aalsmeer and Wenkebach,⁸ Muira³ and Shimazono.⁹ If the changes in blood pressure play a rôle in the cardiac enlargement, they are merely contributory, not primary.

Electrocardiographic Examination.—The results of the electrocardiographic examinations are summarized briefly in table 1. It is remarkable that there were no characteristic changes from the normal. The rate was usually increased. The mechanism was normal in every case, and arrhythmias were not observed, except in one patient who had extrasystoles and sinus bradycardia during convalescence. Right ventricular preponderance was present in two patients.

The height of the ventricular complexes was low in four patients. In these patients, the voltage became higher during convalescence. In

8. Aalsmeer, W. C., and Wenkebach, K. F.: Herz und Kreislauf bei der Beriberi Krankheit, Wien. Arch. f. inn. Méd. **16**:193 (Jan.) 1929.

9. Shimazono: Stepp. Die avitaminosen, Berlin, Julius Springer, 1927.

COMMENT

When the records shown in figure 2 were first examined, it was noted that bundle branch block was no longer constantly present and that the actual transition from aberrant to normal ventricular complexes was illustrated in lead II. Because of the fact that the abnormal ventricular conduction occurred both in the presence of fibrillation of the auricles and more rapid cardiac rate, it seemed of interest to determine which, if either, of these factors was responsible. This was made clear when lead II in figure 3 was examined. Here, though the auricular fibrillation persisted, both normal and aberrant ventricular complexes were present.

From the data thus far collected it was apparent that faulty conduction through the ventricular portions of the bundle bore a certain relation to the cardiac rate. In other words, whenever the period of rest between ventricular systoles was of sufficient length, the intraventricular conduction time was within normal limits, and whenever this period was somewhat shortened, faulty conduction ensued.

To test the validity of this hypothesis, the ventricular rate was slowed by rest in bed and the administration of appropriate doses of digitalis. In a number of records the ventricular complexes were found to be normal, with a cardiac rate of about 60. The rate was then increased by having the patient alternately raise and lower the right leg with the electrodes in place. In figures 4 and 5 it can be seen that with the shortening of diastole a limit was finally reached below which normal conduction through the ventricles no longer occurred.

The interpretation of our observations seems fairly simple, though the exact nature of the underlying disturbance is considerably more complex. In this case a functional derangement of the ventricular conducting system becomes demonstrable only under conditions demanding a more rapid distribution of the excitatory process as the cardiac rate is increased.

That simple asphyxia may in some instances affect intraventricular conductivity has been shown by Lewis⁵ and by Resnik.⁶ In clinical cases Barach and Woodwell⁷ have observed bundle branch block to diminish in degree (records not published) following the inhalation of oxygen. In these experiments, as illustrated in figures 6 and 7, the administration of oxygen brought about a striking improvement in intraventricular conductivity. The aberrant complexes disappeared dur-

5. Lewis: Observations upon Disorders of the Heart's Action, *Heart* **3**:279, 1911-1912.

6. Resnik: Observations on the Effect of Anoxaemia on the Heart, *J. Clin. Investigation* **2**:117, 1925.

7. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determination of the Blood Gases, *Arch. Int. Med.* **28**:367 (Oct.) 1921.

others, the waves which were high during the acute stage of the disease became lower as they improved.

The P-R interval varied from 0.13 to 0.20 second, the average being 0.16 second. In three patients, the P-R interval decreased during convalescence and in one patient it increased.

TABLE 1.—*Electrocardiograms of Patients with Beriberi and Signs of Cardiac Insufficiency*

No.	Rate per Minute	Rhythm	P-R Interval, Seconds	Diagnosis	Remarks
1	107	Sino-auricular	0.20	Normal mechanism; sinus tachycardia; right ventricular preponderance	T ₂ iso-electric; T ₃ negative
2	52	Sino-auricular	0.16	Normal mechanism	P ₂ negative; T ₃ negative; R ₃ notched
3	100	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 3
3a	85	Sino-auricular	0.16	Normal mechanism	R ₃ notched
4	95	Sino-auricular	0.16	Normal mechanism	
5	120	Sino-auricular	0.17	Normal mechanism	R wave notched in all leads
5a	110	Sino-auricular	0.14	Normal mechanism	
6	136	Sino-auricular	0.16	Sinus tachycardia	Died; diaphragmatic paralysis
7	88	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	
8	134	Sino-auricular	0.20	Normal mechanism	
8a	105	Sino-auricular	0.14	Normal mechanism	
9	100	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 1; T ₂ high
9a	88	Sino-auricular	0.16	Normal mechanism	Low voltage in leads 1 and 3; P ₂ flat and T ₃ negative
10	118	Sino-auricular	0.16	Normal mechanism	
11	130	Sino-auricular	0.16	Normal mechanism	Died; pulmonary tuberculosis
12	120	Sino-auricular	0.16	Normal mechanism	T ₃ positive
12a	120	0.16	Normal mechanism	T ₃ negative
b	65	0.16	Normal mechanism	T ₃ negative
c	48	0.12	Normal mechanism	T ₃ positive
d	48	0.12	Normal mechanism	T ₃ positive
13	80	Sino-auricular	0.16	Normal mechanism	
	45	Sino-auricular	0.18	Normal mechanism	Ventricular extrasystole
14	115	Sino-auricular	0.13	Normal mechanism	
15	100	Sino-auricular	0.16	Normal mechanism	T ₂ high
15a	88	Sino-auricular	0.16	Normal mechanism	Low voltage in leads 1 to 3; P ₃ flat; T ₃ negative

In five cases, the T waves were negative in lead 3. In one of these, T₃ became positive during the convalescence of the patient, and in two it became negative. These changes occurred without the use of digitalis. In some cases during the acute stage, the T waves in lead 2 were high, and became lower during recovery.

Aalsmeer and Wenkebach⁸ pointed out that the electrocardiograms of patients with beriberi are normal. They did not observe abnormal rhythms or changes in conduction. There was a tendency for some to show right ventricular preponderance, and the height of the ventricular waves was at least normal or sometimes increased. In some of their

Book Reviews

AN OUTLINE OF ENDOCRINOLOGY. By W. M. CROFTON, B.A., M.D., Lecturer of Special Pathology, University College, Dublin; Pathologist, Dr. Steeven's Hospital, Dublin. Second edition. Price, \$3. Pp. 163, with 53 illustrations. New York: William Wood & Company, 1929.

This book is brief and is clear in diction. Everything else that must be said about the volume is unfavorable. In fact, it is essentially an uncritical propaganda of polyglandular therapy by mouth.

The author states in the preface that "Time is steadily vindicating the effectiveness of the oral administration of endocrine products for therapeutic purposes." The general unreliability of the book is emphasized by the following quotations, picked at random from the several chapters. On page 19, the author states that "pituitrin produces a marked diuresis." The contrary is the case, particularly in diabetes insipidus and when diuresis is produced by liquids by mouth. On page 35, the author says that "Adrenalin is very successful in the treatment of osteomalacia"; and on the following page, "In Addison's disease adrenalin is given by mouth every two hours." Further, "Adrenalin ought to be useful in a condition that results from over-action of the ovarian internal secretion. For instance in menorrhagia and metrorrhagia it might be combined with testicular substance."

On page 57, "Parathyroid extracts twice or three times a day are recommended as efficient in chronic infections." On page 63, the author states that "the thymus gland should always be used in rickets" and "testicular substance or ovarian or both should be extensively used in status lymphaticus, thymic asthma, and myesthesia gravis." On page 73, "For the purpose of increasing lactation, a combination of corpus luteum, mammary substance and placenta may be used. Such combinations are available commercially." On page 76, "Testicular substance (by mouth) is clearly one of the most powerful tonics we possess for both men and women." On page 84, "Spleen extract combined with liver and external ferments of the pancreas can be obtained commercially (Kinazyme) in the form of tablets. 1 to 3 of these can be given three times a day after food. I have found it of the greatest possible use as a routine for improving the nutrition of tuberculous patients."

In the chapter on the pancreas and diabetes the author states: "Insulin is not the only product which controls diabetes. There are several products which have been on the market for several years which, given by mouth, will enable the majority of patients to metabolize sufficient glucose to keep them with a feeling of well-being." On the following page there occurs free advertising of Carnrick's trypsinogen, Fairchild's holadin and the Pan Secretin Company of the Harrower Laboratories as a therapeusis for diabetes.

These quotations suffice to indicate to the informed physician the general unreliability of the book. In the epilogue the author states that "every cell in the body is under the control of the nervous system, under the control of which it carries on its normal activities." As every informed reader knows this is an open question, especially in relation to the endocrine glands, with the exception of the medulla of the suprarenal glands and the production of epinephrine. The author appears to be promulgating all of these therapeutic vagaries or proved errors in all seriousness, but on page 71 there appears to be an indication of Irish wit when he says that "In prima donnas, in whom it is important to preserve the quality of the voice, the use of ovarian substance would be worth a trial." Books of this stripe reflect on the credit of the medical profession of this generation.

cases, the P-R interval was shortened during the acute stage, and became longer during convalescence. I have observed this phenomenon only twice.

Scott and Hermann¹⁰ stated, from the study of their cases, that there were no characteristic or pathognomonic electrocardiographic changes. Although they recognized that the complexes might be small, this was attributed to the presence of subcutaneous edema. They also described negative T waves in leads 1 and 3, and some patients showed a slight to moderate left ventricular preponderance, and some slurring and slight aberration in the ventricular complexes. They were of the opinion that the changes observed were evidences of definite myocardial changes, even in mild cases.

In the case of beriberi reported by Kepler,¹¹ the electrocardiogram was normal.

In summary, then, it may be stated that in the division of patients with cardiac insufficiency there were no characteristic changes in the electrocardiograms, but there was some evidence of myocardial changes in a few.

Roentgen Examination of the Heart.—One of the best methods of studying the changes that occur in the size and configuration of the heart in beriberi is by means of teleoroentgenograms. The results of such a study in a few cases with heart failure are recorded in table 2. The changes in size and configuration can also be seen in charts 1, 2, 3 and 4.

Previous roentgenologic observations of the heart in patients with beriberi were made by Muira,³ Reinhard,¹² Aalsmeer and Wenkebach⁸ and Ido and Watanabe.¹³ Each of these authors called attention to the fact that in many of the patients there is considerable enlargement of the right side of the heart.

In the present study, the diaphragm was examined for mobility, and its level determined on the two sides. The transverse diameter and the width of the shadow cast by the large vessels at the base of the heart were measured. Then, the surface area of the heart was measured

10. Scott, L. C., and Hermann, G. R.: Beriberi (Maladie des Jambes) in Louisiana with Especial Reference to Cardiac Manifestations, J. A. M. A. **90**: 2083 (June 30) 1928.

11. Kepler, E. S.: Beriberi from a Diet of Raw Starch, J. A. M. A. **85**:409 (Aug. 8) 1925.

12. Reinhard, P.: Roentgenbefunde bei beriberiartigen Erkrankungen, Arch. f. Schiffs- u. Tropen-Hyg. **20**:51, 1916; Roentgenbefunde bei Beriberi, Fortschr. a. d. Geb. d. Röntgenstrahlen **24**:104, 1916.

13. Ido and Watanabe: The Orthodiagraphic Examination of the Heart in Beriberi, Sei-i-kwai M. J., Tokyo **33**:35, 1914.

PAIN *

D. C. SUTTON, M.D.

AND

HAROLD C. LUETH, M.S.

CHICAGO

EXPERIMENTAL PRODUCTION OF PAIN ON EXCITATION OF THE HEART AND GREAT VESSELS

In work previously reported,¹ a method has been described for temporary occlusion of the coronary vessels in the unanesthetized dog, and also methods for the study of the production of pain and its transmission. This work was originally begun with the idea of studying the effects of temporary occlusion of the coronary vessels on the supposition that in this way we might simulate angina pectoris, if the theory that angina is produced by a temporary spasm of the coronary vessels is accepted.

As the work progressed, it became necessary to eliminate extraneous causes for pain,² which resulted in the study of pain sensation in the visceral and parietal pericardium, the myocardium and the great vessels, especially the first portion of the aorta. As a result, this investigation developed into three phases: (1) the physiologic effects of temporary occlusion of the coronary vessels in the unanesthetized and anesthetized dog; (2) the study of production of pain in the heart and blood vessels, and (3) the results that were found to follow distention of the aorta, the aortic ring and the peripheral vessels.

THE PHYSIOLOGIC EFFECTS OF TEMPORARY OCCLUSION OF THE CORONARY VESSELS IN UNANESTHETIZED DOGS

Under ether anesthesia, without the use of morphine or any other sedative, and with artificial respiration, the chest was opened in the fifth left intercostal space, exposing the parietal pericardium. Through a small incision in the parietal pericardium, a ligature was passed around the ramus descendens anterior sinister branch of the left coronary artery; without being tied, this ligature was passed through a flanged

* Submitted for publication, Oct. 25, 1929.

1. Sutton and King: Physiological Effects of Temporary Occlusion of the Coronary Vessels, *Proc. Soc. Exper. Biol. & Med.* **25**:842, 1928. Sutton, D. C.: Studies of the Mechanism of the Production of Cardiac Pain, *Tr. Institute of Med., Chicago*, February, 1929.

2. Pain is presumed to be present when a trained animal otherwise quiet becomes restless, moves and gives other evidence of distress during any procedure.

TABLE 2.—*Röntgen Examination of the Heart in Patients with Beriberi and Signs of Cardiac Insufficiency*

Patient	Day of Observation	Diaphragm				Transverse Diameter, Cm.			Surface Area of Heart				
		Motility (Fluoroscopic Examination)	Position		To Right of Mid-sternal Line	To Left of Mid-sternal Line	Total	Estimated Measured		Oversize, Sq. Cm.	Aorta, Cm.		
			Right	Left				Sq. Cm.	Sq. Cm.				
1	1st day	Movement normal	10th rib	10th rib	5.6	10.7	16.3	107.56	157.3	49.74	6.4		
	8th day	Movement normal	10th rib	10th rib	4.4	9.3	13.7	104.07	131.9	27.83	5.9		
	10th day	Movement normal	11th rib	11th rib	3.7	8.9	12.6	104.01	124.8	27.90	5.6		
2	1st day	Movement normal	10th rib	3.4	12.3	15.7	98.11	132.0	44.10	5.5		
	14th day	Movement normal	10th rib	10th rib	3.9	10.0	13.9	96.00	118.5	22.50	4.0		
	24th day	Movement normal	10th rib	10th rib	3.3	9.6	12.9	96.00	118.2	21.00	4.8		
3	1st day	Movement normal	9th rib	4.9	10.5	15.4	98.56	124.0	25.44	6.0		
	7th day	Movement normal	9th rib	10th rib	4.0	8.8	12.8	96.00	106.5	10.00	4.8		
	24th day	Movement normal	10th rib	10th rib	3.2	8.9	12.1	96.00	106.5	10.00	4.8		
4	1st day	Movement normal	10th rib	4.0	10.1	14.1	104.01	126.2	22.00	4.8		
	15th day	Movement normal	10th rib	11th rib	4.1	8.3	12.4	104.01	106.5	2.00	5.0		
5	1st day	8th rib	3.8	8.4	12.2		
	27th day	9th rib	3.0	7.5	10.5		
6	1st day	Movement normal	9th rib	10th rib	5.2	10.2	15.4	95.10	146.5	51.00	5.5		
7	1st day	9th rib	5.5		
	14th day	9th rib	10th rib	6.4	7.7	14.1	92.00	99.0	7.00	5.0		
8	1st day	Movement normal	8th rib	3.8	8.0	11.8		

Electrocardiographic tracings taken from lead II show a normal rate of 128 with an R wave 3.8 millivolts in height, and a T wave 0.6 millivolts in height. On the first traction an immediate paroxysmal attack of premature contractions of ventricular origin was seen, with a rate of 150. On second traction there were pauses of a second's duration, followed by rapid premature contractions of ventricular origin. The T wave was 1.4 millivolts. The third traction produced immediate paroxysms of premature contractions of ventricular origin, showing an average T wave 1.6 millivolts in height. The fourth traction resulted in complete cardiac standstill for five seconds. The fifth traction resulted in pauses of one second's duration. In no lead was there an inversion or change in the T wave other than that of increase in height.

After completion of the experiment, the chest was opened under general anesthesia; the pericardium was found to be distended and tense, so that on opening, the heart bulged through. All chambers of the heart were greatly distended. The location of the ligature was verified, the artery being torn in two, one-half inch distal to its origin.

Dog 2.—The operation was done as in the preceding experiment. Four hours after completion of the operation, the animal was in excellent condition, running about the room and giving no evidence of pain. It lay quietly until traction was made on the ligature, which produced moderate pain, restlessness and increased respiratory movements. The pulse increased in size and in rate at the beginning of the contractions, and there were frequent premature contractions. On prolonged traction, the pulse became more rapid and smaller. Pain ceased promptly with cessation of traction. Traction was repeated many times with the same results.

On opening the chest under anesthesia, all chambers of the heart were found to be dilated. The ligature was found to include the vein only. (Therefore occlusion of the coronary vein accompanying the ramus descendens anterior sinister produced pain.)

Dog 3.—The dog was operated on as in the preceding experiments. Five hours were allowed for recovery. The dog was in good condition, apparently suffering no pain. Traction produced immediate pain followed by rapid irregular pulse and salivation. During traction, along with the marked respiratory stimulation (fig. 2) there was a marked sinus arrhythmia. The pain ceased promptly on release of traction. After several temporary occlusions, 3 mg. of atropine sulphate was injected intravenously. The atropine greatly increased the pulse rate and caused complete disappearance of the sinus arrhythmia. Slight traction produced marked pain, which disappeared promptly on cessation of traction.

On opening the chest under general anesthesia, moderate dilatation of all chambers of the heart was found. The ligature was found to be around the artery and vein, three fourths of an inch distal to its origin.

Dog 4.—The animal was prepared as in the preceding cases and allowed four hours for recovery. The condition was good, with apparently no pain. Traction produced immediate pain with salivation, the pain ceasing when traction was released. Pain appeared to vary with the degree of traction. The animal vomited during traction.

The electrocardiogram shows a normal rate of 132, with an R wave in lead II of 1.5 millivolts, and a T wave of 0.5 millivolts. The wave was notched in lead II. First traction produced only an increase in rate; the second traction increased the rate to 168 per minute, with pauses of from one to one and one-half seconds' duration. The T wave was 0.7 millivolts and was not notched. The third traction produced a pause of one and one-half seconds' duration. The T wave was notched 0.4 millivolts. The fourth traction produced a rate of 168. The T wave

according to the method described by Hodges and Eyster,¹⁴ and the variation from normal calculated in square centimeters.

There was an enlargement of the heart in all cases. It was due principally to an increase in the size of the right auricle and right ventricle. The right ventricle was enlarged outward and upward, and the right auricle was increased outward.

Another striking feature was an increase in the shadow in the region of the pulmonary artery. This was undoubtedly due to an increase in the size of the conus arteriosus and the pulmonary artery.

Besides these changes, the shadow of the vessels at the base of the heart was often increased, particularly to the right. This was due to an increase in the shadow cast by the superior vena cava. It can be readily seen in the x-ray picture taken in case 4.

The left auricle and the left ventricle shared to a less extent in the cardiac enlargement, since examination of the heart in the left and right anterior oblique positions revealed only moderate enlargement of these structures.

The size and configuration of the heart was followed by repeated roentgen examinations during the course of the illness, and interesting changes were observed. The heart decreased in size in a short time, and the configuration became that of a normal heart. The shadow of the vessels at the base also decreased, and the pulmonary artery became less prominent.

In summary, it may be stated that roentgen examination of the heart recorded a change in the size and configuration of the heart in these patients. The enlargement was due to an increase in the right auricle and the right ventricle, the pulmonary artery and the superior vena cava. A decrease in the size of the heart occurred rapidly following proper therapy.

The cases herein reported illustrate the various changes that may occur.

REPORT OF CASES

CASE 1.—History.—A Chinaman, aged 18, was first seen in the outpatient department of the Peiping Union Medical College one month before admission to the hospital. He complained of swelling of the legs and face. His previous history was unessential.

He had always enjoyed excellent health until one week before coming under observation. At that time, he began to notice excessive fatigue on exertion, and edema of the lower extremities. He had palpitation after walking, but little shortness of breath; otherwise he felt well.

14. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, *Am. J. Roentgenol.* **12**:252 (Sept.) 1924.

was notched at times, almost iso-electric. The R wave was 4.8 millivolts. The fifth traction T wave was 1.2 millivolts and was notched. The P wave arose from the down strokes of the T.

Opening of the chest under ether anesthesia revealed moderate dilatation of all chambers of the heart, the ligature surrounding the artery one-half inch distal to its origin.

Dog 6.—The animal was prepared as in the preceding experiments, and about three hours were allowed for recovery. Slight traction produced pain and marked respiratory stimulation. Strong traction produced severe pain. The pain ceased immediately on cessation of traction.

The electrocardiogram showed a normal R wave of 1.6 millivolts, and a T wave of 0.3 millivolts. The rate was 168. The rate following the first traction was 168, with marked arrhythmia of the sinus, the T wave rising sharply from the down stroke of the R wave. The T wave was 0.4 millivolts; the P wave, 0.4 millivolts. On second traction, the R wave was 2.4 millivolts; the T wave, 1.6 millivolts, and the P wave, 1.2 millivolts. The rate was 144. Following the third traction, the R wave was 2 millivolts; the T wave, 2 millivolts, and the P wave, 1.4 millivolts. The T wave was notched on the ascending limb; the rate was 144. This dog was allowed to live two days. On the second day, traction produced pain. The location of the ligature was verified at autopsy, one-fourth inch distal to the origin of the artery, the animal having died of pericarditis.

Dog 8.—The dog was prepared as those in the preceding experiments, with the exception that the ligature was passed around a small branch of the ramus descendens anterior sinister. A second ligature was passed so as to include only muscle and pericardium, this ligature being passed through the same tube. Recovery was good. Traction of the ligature on the artery produced moderate pain, giving the impression that the severity of the pain may be in relation to the size of the artery occluded. The suture placed only in the muscle produced no pain on traction. Traction on each ligature was repeated many times with a constant repetition of the result. Finally the ligature in the myocardium tore through the muscle and pericardium without producing pain.

Autopsy verified the location of the first ligature around a small branch, and also showed that no vessel of macroscopic size was included in the second ligature. There was no increase in the size of the cardiac cavities.

Dog 10.—The animal was prepared as in the preceding experiment (dog 8), with one ligature around the artery near its origin, another including the muscle only. There was marked salivation for a period of one hour during recovery. Traction on the artery produced pain repeatedly. Traction on the muscles produced no pain.

Dog 5.—The animal was prepared as dog 1, with the exception that both vagi were severed during the operation. The animal was allowed four hours for complete recovery, and was in good condition except for a moderate cyanosis due to a partial pneumothorax.

Traction produced pain immediately, which ceased on release of traction; salivation was marked. Repeated tractions gave the same result. Under general anesthesia the chest was opened, and the heart was found to be greatly dilated in all chambers; the ligature was found to be around the vein only, one-half inch from the ramus descendens anterior sinister.

The anoxemia from the pneumothorax is believed to be a factor in the production of the great dilatation of the whole heart.

Examination.—On examination, he was found to be well nourished and well developed, and did not appear acutely ill. There was no fever. The mucous membranes were normal. There was moderate edema of the face, legs and thighs. The lungs were clear. The heart was enlarged. The cardiac dulness extended 10.5 cm. to the left of the midsternal line in the fifth intercostal space, and 5.5 cm. to the right in the fourth intercostal space. There were no shocks or thrills; the point of maximum impulse was diffuse and rather feeble. There was a systolic murmur at the apex and over the pulmonic area, and the pulmonary second sound was accentuated. There were no diastolic murmurs. The blood pressure was 116 millimeters of mercury systolic, and 46 diastolic. The pulse was collapsing in type, and one could observe distinct capillary pulsation in the nail beds. The liver was not enlarged and there was no ascites. The knee and ankle jerks were not obtained. The Wassermann reaction of the blood was negative. The urine showed a small amount of albumin but no casts.

The patient refused to enter the hospital, but returned to the outpatient clinic at different intervals for twenty-seven days. During this time, in spite of a limitation of his activities and the administration of digitalis, he became progressively worse. The edema increased, the pulse pressure became higher, the heart rate became more rapid and the liver became enlarged.

Later, on admission to the hospital, he appeared comfortable at rest, although a generalized anasarca was present. There was neither orthopnea nor cyanosis. There was moderate engorgement of the cervical veins, and accentuated pulsation of the peripheral vessels. There was evidence of a pleural effusion on the right side, and a moderate amount of free fluid in the peritoneal cavity. The pulse, collapsing in type, was increased in rate, and the rhythm was regular. There was distinct capillary pulsation, and the arterial sounds over the large vessels were rather loud.

Examination of the heart at this time revealed the apex impulse to be in the fifth intercostal space 13 cm. to the left of the midsternal line. It was diffuse and forceful. By percussion, the heart was found to be enlarged to the left and right of the midsternal line; the transverse diameter measured 16 cm. There were loud systolic murmurs at the apex and over the pulmonic areas, and the pulmonary second sound was accentuated. The blood pressure was 150 millimeters of mercury systolic and 60 diastolic. The lungs did not show any signs of pulmonary congestion. The liver was enlarged. The knee and ankle jerks were absent. There was mild hypesthesia to touch, pain and vibration over the legs. The muscular power was good, except in the anterior tibial muscles, where there was a slight weakness.

There was no anemia. The urine was normal and the phenolsulphonphthalein test showed an excretion of 55 per cent in two hours. There was a normal gastric acidity after the administration of beta-iminazoly-ethylamine hydrochloride. The basal metabolic rate was -8.4 per cent and the nonprotein nitrogen of the blood was 35.4 mg. per hundred cubic centimeters.

The course of illness can be followed by means of chart 1. It may be seen that as long as the patient remained ambulatory, the cardiac rate was high, the edema increased, the systolic blood pressure and the pulse pressure both increased, the size of the heart increased and the symptoms of the patient became worse. There were definite changes in the electrocardiographic tracings, and digitalis caused no improvement. With rest in bed and an adequate diet, supplemented by 3 Gm. of yeast daily, a most remarkable change in the clinical picture was produced. The cardiac rate decreased, the systolic blood pressure fell, the diastolic pressure rose, and there was a marked diuresis with a corresponding loss in weight. The heart decreased markedly in size. The electrocardiographic trac-

4. Pain has been pronounced in every experiment, but there is some variation in the degree of pain in various animals. This variation may be due to one of two causes: first, some animals are less sensitive to pain than others; second, in some dogs' hearts there is a large anastomosing artery between the anterior descending and the circumflex arteries. This anastomosis occurs distal to the point of the ligature, usually through the first branch, to the left toward the apex, of the ramus descendens anterior sinister. This anastomosis is sufficiently large to prevent at times the formation of an infarct when the artery is tied proximal to it.

5. In two experiments, dogs 2 and 5, the vein only was included in the ligature. In these instances the pain was of the same character as in the other experiments, and the fact that the vein only was included in the ligature was not suspected until it was observed at autopsy.

6. The pain produced by compression of the artery and vein is not produced by compression of the muscle and visceral pericardium included in the ligature. This is definitely shown by the failure to produce pain by ligatures passed so as to compress only muscle and visceral pericardium. Even the tearing of the muscle and visceral pericardium when the ligature is pulled until it cuts entirely through both fails to produce pain.

7. When the traction is sufficiently forceful to tear out the ligature, the pain ceases immediately. Explanation for this cessation of pain is offered subsequently.

8. Salivation, which is accepted as evidence of nausea in the dog, has been observed repeatedly during the periods of compression. Dog 4 vomited at the time of complete occlusion of the vessel.

9. Respiration becomes increased in rate and volume as the pain increases, finally becoming violent and irregular. A symptomatic dyspnea is the first evidence of compression and may be the only evidence of moderate occlusion.

10. Section of the vagi or their paralysis with atropine interferes in no way with the production of pain by occlusion of the artery. Respirations were of the type following vagal section, and were unaffected by occlusion of the coronary artery. After vagosection, salivation occurred during traction.

11. Removal of the annulus of Vieussens completely abolishes all pain produced by compression of the vessels, although salivation may occur. Respiration is unaffected.

After repeated temporary occlusion of the vessels, when the dog is killed for autopsy (which is done in every experiment), the heart is found to be increased in size in all its chambers ("acute dilatation"). The degree of dilatation varies in different animals. This variation may

ings changed, and the patient became symptomatically well. With the decrease in the size of the heart and with the changes in the blood pressure, the murmurs, the peripheral pulsation, the capillary pulse and the pistol shot sounds disappeared. The knee jerks did not return while the patient was under observation.

Summary.—A young man showed a gradual development of edema of the extremities and face, with signs of cardiac enlargement, valvular insufficiency and tachycardia, changes in the blood pressure, peripheral pulsation, capillary pulsation, pistol shot sounds over the large vessels, and signs of congestive heart failure which were predominantly of the right side. He failed to improve on a restriction of his activities and the administration of digitalis, but with rest in bed and an antiberiberi diet supplemented by 3 Gm. of yeast daily, all the signs of cardiac insufficiency disappeared. The disturbances of the nervous system were mild and persisted longer than the cardiac symptoms.

CASE 2.—History.—A Chinaman, aged 19, complained of weakness, numbness and swelling of the lower extremities. His previous health had been good until three months before he came under observation. At that time, he began to notice some edema of the ankles and numbness of the legs. Three weeks before admission, the edema increased, and he began to have dyspnea, on moderate exertion, and palpitation of the heart.

Examination.—On examination, he appeared comfortable at rest, and there was no dyspnea, orthopnea or cyanosis. There was moderate edema of the face with engorgement of the veins of the neck, and the pulsation in the vessels of the neck was forceful. The heart was enlarged. The cardiac dulness extended 12 cm. to the left of the midsternal line in the fifth intercostal space, and 3 cm. to the right in the fourth intercostal space. There was a loud systolic murmur at the apex and over the pulmonary area, and the pulmonary second sound was accentuated. The blood pressure was elevated—150 millimeters of mercury systolic and 100 diastolic. The lungs were clear. There was a slight enlargement of the liver. There was edema of the legs, with some tenderness of the calf muscles and a loss of the knee and ankle jerks. There was slight hypesthesia to touch and pain over the legs. It was especially noteworthy that the gait and muscular power were normal.

There was no anemia, the urine was normal and the excretion of phenolsulphonphthalein was 70 per cent in two hours. The electrocardiogram showed a normal mechanism, with negative P and T waves in lead 3. The Wassermann reaction was negative.

The course of the patient's illness can be followed by means of chart 2. It is evident that the cardiac rate decreased, the body weight diminished, the edema disappeared, the blood pressure became lower, the heart decreased in size, and there was a corresponding improvement in the patient's symptoms. The murmurs over the heart disappeared and the patient became symptomatically well, although the deep reflexes did not return while he was under observation. All these changes occurred with rest in bed and an antiberiberi diet supplemented by 3 Gm. of yeast daily.

Summary.—A youth who had lived on a diet of rice with a few green vegetables showed an increasing edema, mild neuritis and cardiac insufficiency. On examination, he had signs of a heart failure on the right side, cardiac enlargement and valvular insufficiency, all of which disappeared after dietary treatment. One of the important features of the illness was the presence of cardiac insufficiency with mild neurologic disturbances.

Both vagi were sectioned. As a result, traction failed to lower the blood pressure. Ventricular amplitude was increased, but the rate was the same throughout for the auricle. The apex of the left ventricle became cyanotic. Both auricle and ventricle were increased in volume during traction (fig. 3).

Dog 102.—The animal was prepared as was dog 100. Traction caused first a decrease and then an increase in auricular amplitude. The ventricle was less affected than in the preceding experiment. The blood pressure fell slowly but definitely. Respiration was increased in amplitude and rate, as shown by increased diaphragmatic movements recorded by pneumograph attached to the abdomen. The tip of the ventricle became cyanotic during traction, and both ventricle and auricle became increased in volume. Attempted ligation of the circumflex failed, due to laceration of the arterial wall with hemorrhage. Following this there was a great increase in blood pressure, and the heart dilated slowly.

At autopsy it was found that there were three coronary arteries: the anterior descending and the circumflex which consisted of two separate arteries with two orifices. The anterior descending was surrounded by the ligature.

Dog 103.—With the dog under barbital ether anesthesia, preparation was made as in the experiment with dog 100. The ligature was placed around the ramus descendens anterior sinister, three eighths of an inch below its origin. Tracings of the auricle and ventricle were poor because of mechanical difficulties. Traction caused decrease of amplitude of the auricle with later increase. The ventricle dilated with premature contractions. At the beginning of traction the rate was increased, followed by increase in amplitude. The blood pressure fell with each traction. The vagi were sectioned during traction. The cardiac rate was increased. Only a slight fall in blood pressure occurred and was maintained at the lower level. Before section of the vagi, respiration (recorded as in the preceding experiment) increased in rate and decreased in amplitude. This rate continued after the first traction and did not change until after the vagi were severed. The apex of the left ventricle became cyanotic, and dilatation promptly followed traction (fig. 4).

Dog 104.—With the animal under barbital ether anesthesia, it was prepared as was dog 100. The left ramus descendens anterior sinister was ligated one-fourth inch below the bifurcation. With a slight increase in auricular amplitude during the traction, the ventricle became cyanotic over the area supplied by the artery with only slight dilatation during traction. Premature contractions were produced at the beginning and end of traction, ventricular amplitude being increased throughout traction. The blood pressure showed a moderate fall with each temporary occlusion. Both vagi were sectioned during traction, which was followed only by a moderate fall in blood pressure. The animal was allowed to become anoxic by shutting off the artificial respiration which resulted in marked increase of irritability of the heart muscle during traction and greatly increased fall in blood pressure. Four cubic centimeters of digitalis was injected intravenously which resulted in no change following traction further than increased muscular irritability. Respiration showed no change during traction (fig. 5).

Dog 105.—The dog was prepared as the others of this series, the ligature being passed around the left ramus descendens. Traction produced marked fall in blood pressure. The ventricular wall included in the distribution of the artery became markedly cyanotic, but no dilation of the ventricle occurred. Increased amplitude of both auricular and ventricular contractions during traction was noted. Respiratory movements were increased during traction. The annulus of Vieussens was removed. During traction the blood pressure fell. The left vagus was severed, following which there was only a slight fall of blood pressure on temporary occlu-

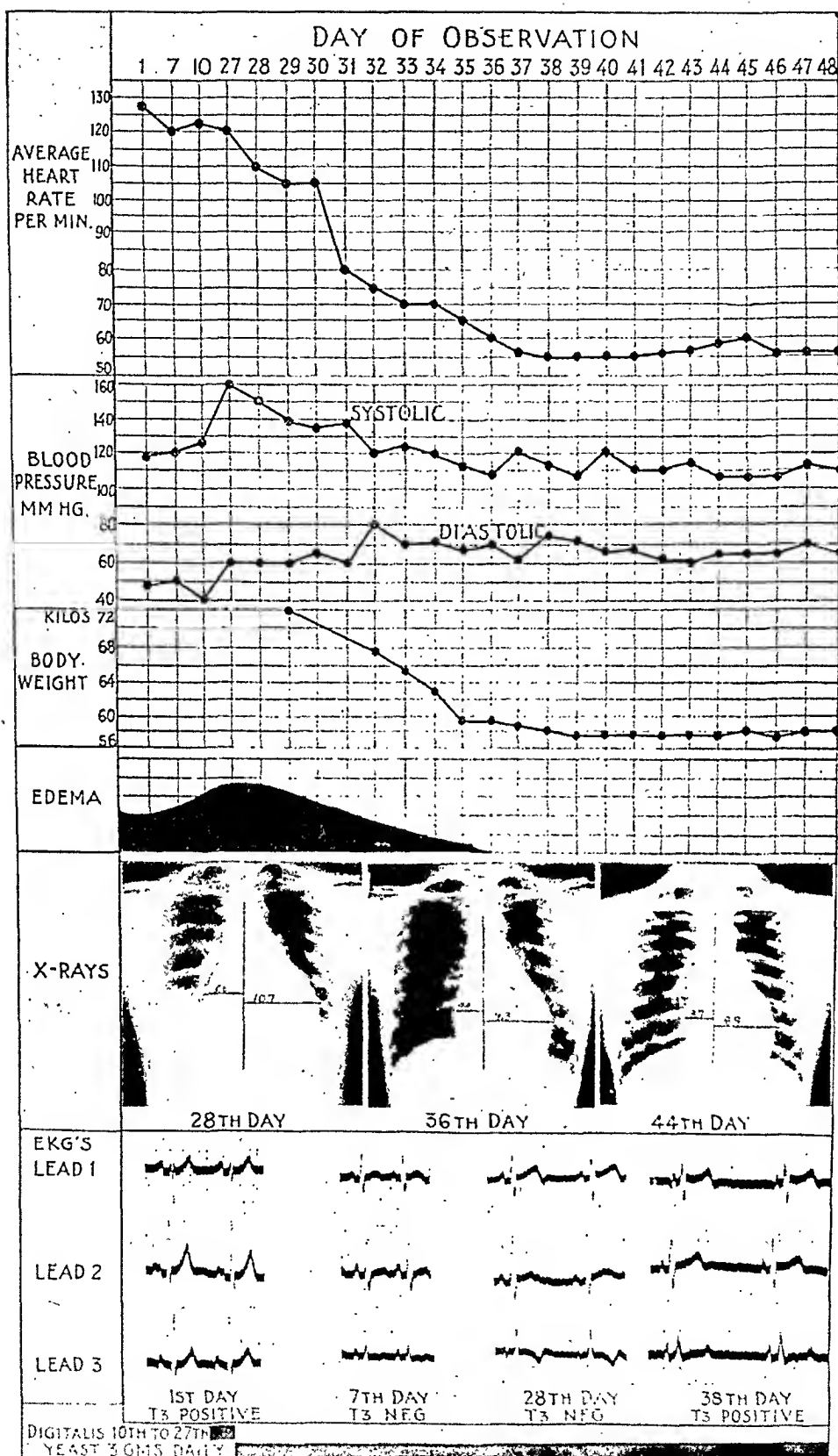


Chart 1 (case 1).—Results of examinations made during the upward course of the illness, and on treatment with rest in bed and an antiberiberi diet.

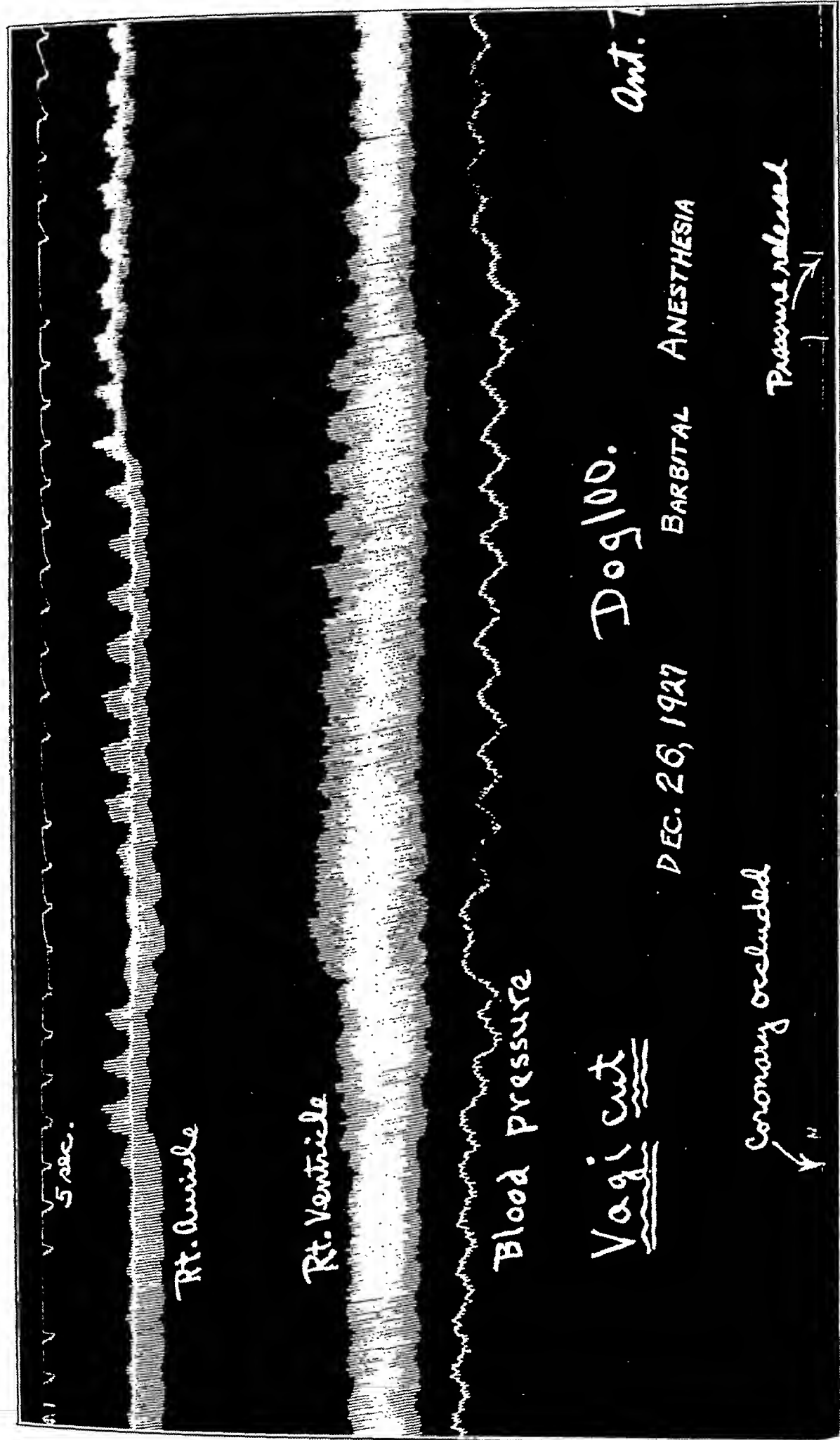


Figure 3

Fig. 3.—Curve for dog 100. There was a fall of blood pressure of 40 mm. of mercury. No fall occurred after section of the vagi.

CASE 3.—*History*.—A Chinaman, aged 19, was admitted to the hospital complaining of a swelling of the legs and ankles that had endured for three weeks, and moderate shortness of breath after exertion that had endured for one week. For about eight months he had been living on a diet consisting chiefly of boiled rice and vegetables. His symptoms had begun insidiously without any signs of cardiac insufficiency. He first had noticed swelling of the legs. Following the

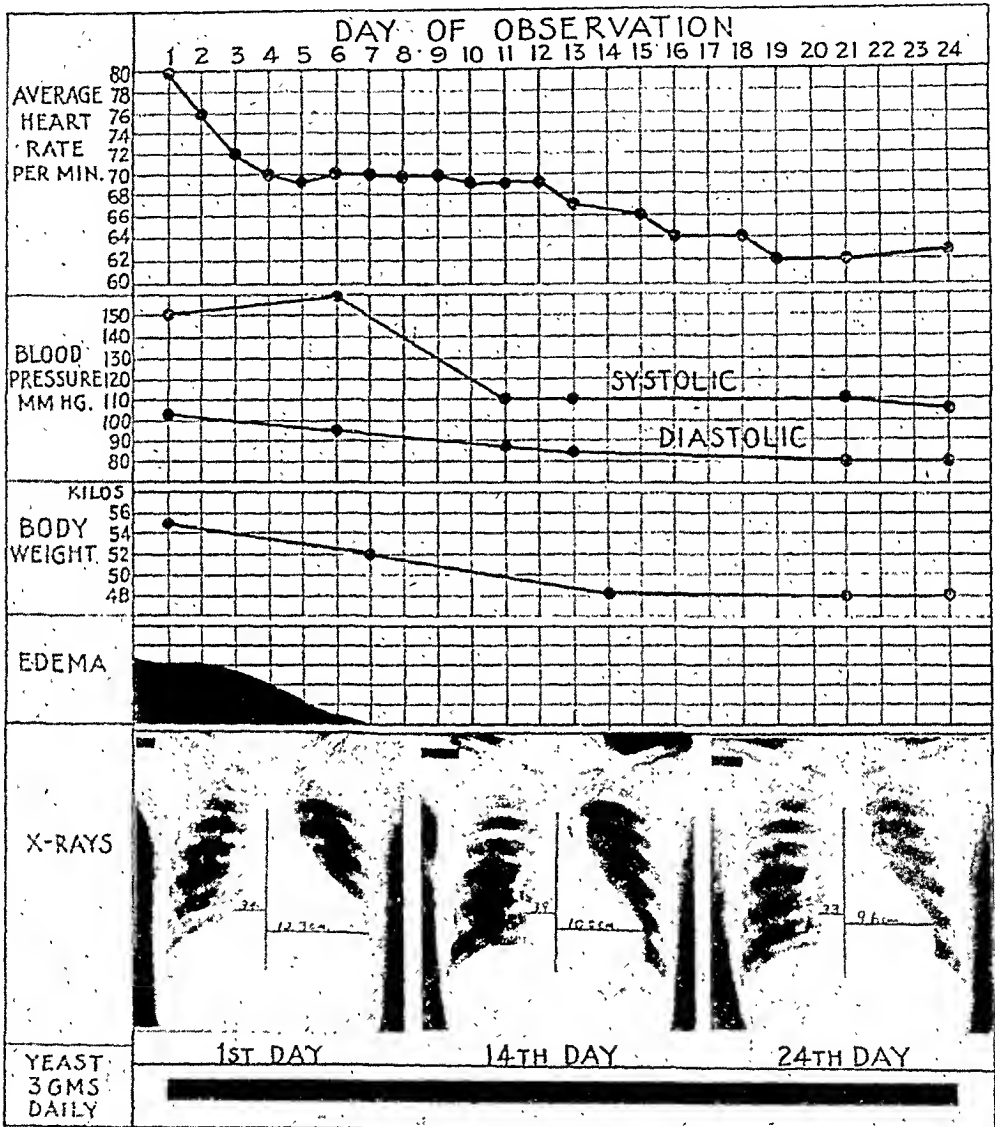


Chart 2 (case 2).—Improvement in beriberi with cardiac insufficiency when patient was at rest in bed and on antiberiberi diet.

appearance of the edema, he had begun to have shortness of breath and palpitation on exertion.

Examination.—On examination, he appeared comfortable at rest. There was no dyspnea, orthopnea or cyanosis. There was engorgement of the cervical veins with slight puffiness of the face. The lungs were clear. The heart was enlarged. There was a systolic murmur at the pulmonic area. The sounds at the apex were clear. The blood pressure and the pulse were normal. The liver was enlarged,

sion of the artery. The auricle and ventricle fibrillated for a short period spontaneously and then returned to normal rhythm.

Dog 106.—The animal was prepared in the same way as dog 105. The first traction produced a sharp fall in blood pressure of 48 mm. of mercury, with short ventricular standstill. Later tractions showed less change in blood pressure, but greater ventricular and auricular irritability.

Removal of the left stellate ganglion caused disappearance of the fall of blood pressure on traction, but the second traction produced greater irritability and increased amplitude of both auricular and ventricular tracings. After cutting of the left vagus this increased irritability and increased amplitude were not evident. Anoxemia caused lessened amplitude with increase in rate during traction, with greatly increased amplitude after release of traction. Final permanent occlusion produced auricular and ventricular fibrillation. Anoxemia greatly increased the dilatation of all cavities during traction.

SUMMARY AND CONCLUSIONS

Compression of the artery, vein and included tissue produces first a cyanosis of that portion of the ventricle supplied by the vessels; the vein becomes distended, while the myocardium becomes definitely paler. Almost immediately there is a definite and at times a marked increase in the volume of both ventricles and later also the auricles. Immediately following partial compression of the vessels there is a definite, rapid fall in blood pressure, amounting to from 30 to 50 mm. of mercury. Marked irregularities occur, as: (1) temporary ventricular standstill or cardiac standstill followed by many premature contractions, usually of ventricular origin, but also often of auricular origin; (2) paroxysmal tachycardia of both ventricular and auricular origin; (3) auricular fibrillation; (4) ventricular fibrillation; (5) "acute dilatation" of all the chambers of the heart; this is increased by anoxemia. With section of the vagi, compression does not result in any fall in blood pressure, except such fall as may occur as a result of ventricular or cardiac standstill.

Symptoms analogous to those occurring in man in angina pectoris and coronary occlusion can be produced experimentally in the dog; namely, pain, sometimes nausea and vomiting, stimulation of respiration and fall in blood pressure. Pain is abolished by removal of the annulus of Vieussens. It is suggested that sudden death in angina pectoris may be the result of ventricular fibrillation occurring during temporary decrease in coronary flow.

PRODUCTION OF PAIN BY EXCITATION OF THE PERICARDIUM, HEART AND GREAT VESSELS

As shown in the preceding paragraphs, temporary occlusion of a branch of the coronary artery alone or a coronary vein alone or of the two together invariably produces immediate, and in the larger vessels severe, pain. This pain disappears immediately on release of com-

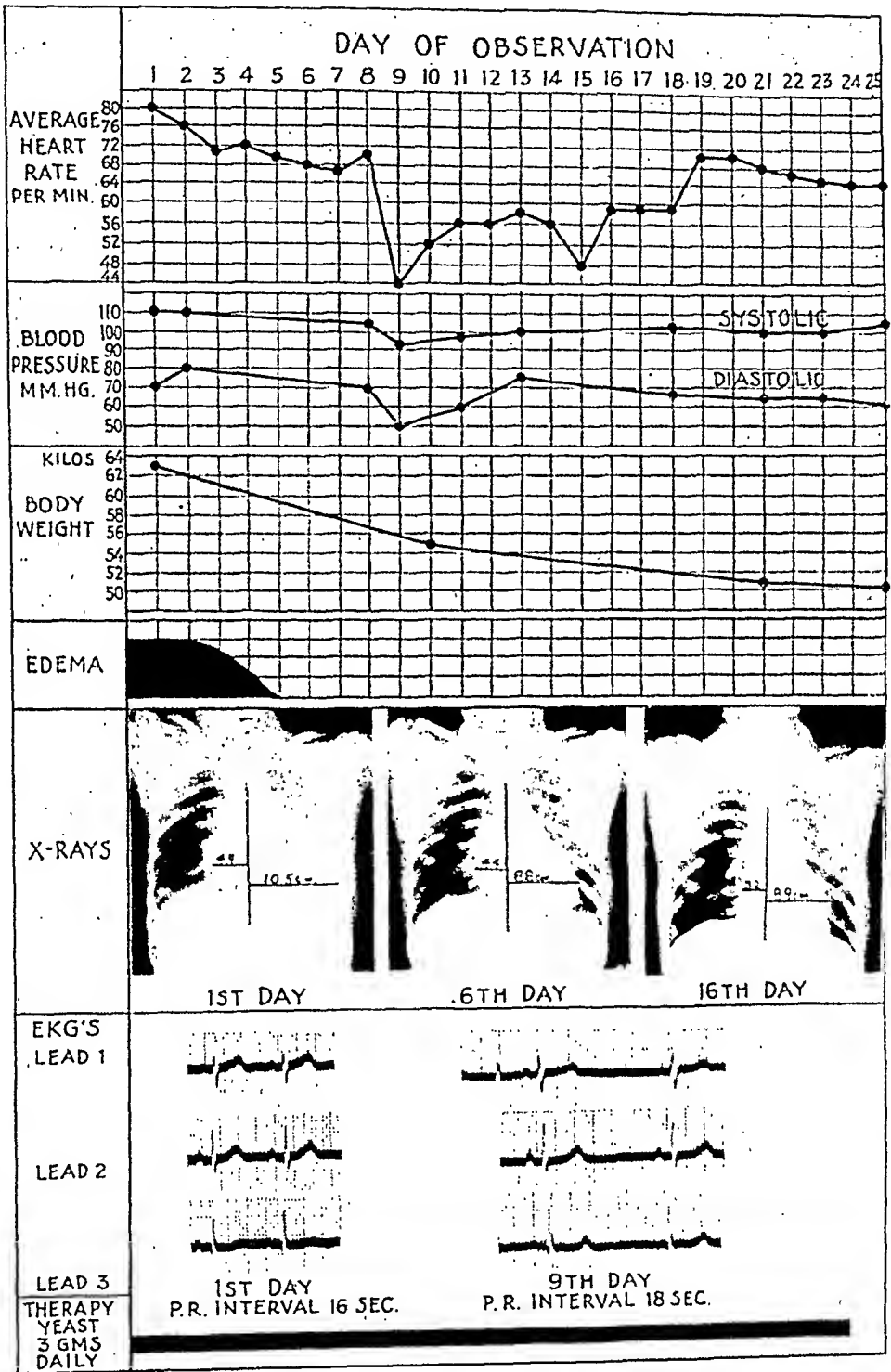


Chart 3 (case 3).—Effect of rest in bed and an antiberiberi diet on patient with beriberi and cardiac insufficiency.

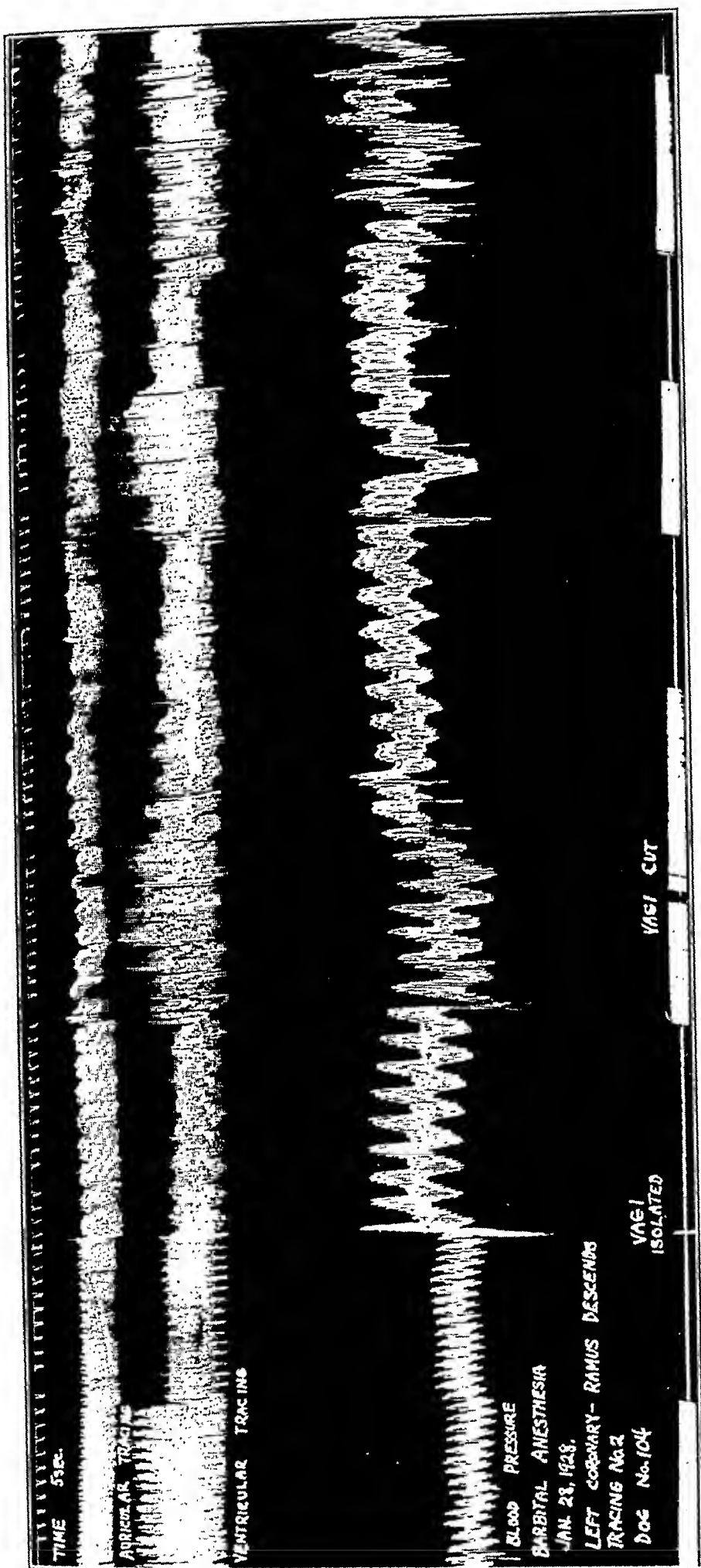


Figure 5

Fig. 5.—Curve of dog 104. In tracing no. 1, the changes in the ventricular rhythm and amplitude should be noted; in no. 2, the effect of section of the vagi is shown.

and there was edema of the legs. The knee and ankle jerks were absent. There were no sensory disturbances and the muscular power, it is to be noted, was normal.

The Wassermann reaction was negative. There was no anemia. The urine was clear. The excretion of phenolsulphonplithalein was .55 per cent in two hours. The x-ray pictures and electrocardiograms are shown in chart 3.

Chart 3 illustrates the course of the illness. It may be seen that the rate was never excessively rapid, but with improvement it became slow. The blood pressure decreased, the weight diminished and the edema disappeared within five days. The heart likewise decreased in size, and the electrocardiogram changed. The knee jerks did not reappear while the patient was under observation.

Summary.—A young man showed a development of the symptoms and signs of cardiac insufficiency with mild neurologic disturbances. All the signs of heart failure subsided rapidly following an adequate diet supplemented with yeast.

SUMMARY OF OBSERVATIONS IN CASES OF BERIBERI WITH CARDIAC INSUFFICIENCY

In regard to the clinical features of the patients who had cardiac insufficiency, it may be said that most of them complained of palpitation, edema and some shortness of breath on exertion. These symptoms sometimes were preceded by pains in the calf muscles. If the patient was seen early in the course of his illness, it was noted that the heart rate was somewhat accelerated. The blood pressure might be normal. There were no conspicuous changes in the peripheral vessels. The heart was enlarged both to the right and to the left of the midsternal line; the apex beat was diffuse, and not forceful. There was usually a systolic murmur over the pulmonary area, and the pulmonary second sound was accentuated. The lungs did not show signs of congestion, and the liver was not enlarged. There was usually edema of the lower extremities.

As the disease progressed, all these signs became exaggerated and the edema increased. The liver became enlarged, and nausea and vomiting sometimes appeared. Striking changes occurred in the peripheral circulation. There might be increased peripheral pulsation of the vessels of the neck and extremities, with a collapsing type of pulse and capillary pulsation. The sounds over the brachial and femoral arteries were increased. Examination of the heart revealed an increased enlargement with a systolic apical thrill, and loud systolic murmurs over the mitral and pulmonary areas. The rhythm, however, remained regular and it seemed clear that the common arrhythmias do not occur in this disease. Teleoroentgenograms of the heart revealed enlargement of the right auricle and the right ventricle, with a prominent pulmonary artery and a prominent superior vena cava. The electrocardiograms did not show anything characteristic. The voltage might be low or high. Minor abnormalities, such as changes in the T waves, might be present.

All these conditions might occur in the cardiovascular system with slight changes in the nervous system. The latter generally consisted of minor sensory disturbances and a loss of the knee and ankle jerks.

Summary.—From these experiments (dogs 200 to 210 inclusive) it appears that the pain fibers involved in experimental occlusion of the coronary artery are the nerve fibers that are found in the adventitia of the coronary artery or in the immediate surrounding tissues, and that the cutting of this pathway prevents the transmission of pain, which appears to be produced in the temporarily infarcted area of the heart muscle. This dissection of the fibers with the resultant cessation of pain explains the similar condition noted when the artery and vein were torn through by the ligature; namely, that the pain pathway is severed. The disappearance of pain after the tearing through of the artery and vein is also evidence against the fact that the pain may be produced in occlusion by the sudden distention of the artery proximal to the point of occlusion.

These experiments do not exclude entirely the possibility that pain is due to compression of the nerves. To eliminate that possibility, in two dogs the ramus descendens anterior sinister was injected with mercury at a point near its origin. In one, the mercury lodged at the first branch and was included in a firm thrombus. In the second, no mercury was found, but the artery as a result of injury was also filled with a firm thrombus. In both, an anemic infarct was found. On recovery, no objective evidence of pain was shown by either dog. Both were exercised by running until greatly fatigued, without the production of pain. This may be explained either on the ground that pain does not persist during the period required for the dog to recover from the anesthesia, which would be comparable to the cessation of pain in coronary thrombus in man, or more likely by the fact that dogs do not show evidence of continuous pain, unless extremely severe, in any manner like that resulting from a sudden pain.

The results of these two experiments did not assist in answering the question at hand; so no further experiments were performed.

Dog 300.—The chest of this dog was opened, and an incision was made through the parietal pericardium. An angulated needle was introduced into the ramus descendens, one-fourth inch from its origin, the point being passed toward the periphery. Three cubic centimeters of mercury was injected, the pericardium was sutured and the animal was allowed to recover as in preceding operations.

This dog was excited postoperatively, and was greatly salivated during the period of recovery. After recovery the animal apparently suffered no inconvenience. He was run approximately four blocks, at the end of which he collapsed with a rapid imperceptible pulse, but apparently suffered no pain. One hour later, he could not be tired by running.

With the animal under general anesthesia, the chest was opened, the right ventricle being found apparently contracted to a smaller size than normal. There was an area of definite anemia in the area supplied by the artery beyond the first branch after its origin. A drop of mercury was found at this branch firmly embedded in a thrombus.

When the patient was treated with rest in bed and an antiberiberi diet supplemented with yeast, striking changes occurred. The heart rate fell, the blood pressure became normal, the peripheral pulsation and the collapsing and capillary pulse disappeared, diuresis set in, the heart became smaller, the murmurs disappeared and the patient became normal. The deep reflexes did not reappear until many weeks after the cardiac signs disappeared.

PATIENTS WITHOUT CARDIAC INSUFFICIENCY

In contrast to the patients with cardiac insufficiency, those without cardiac insufficiency complained chiefly of symptoms referable to the nervous system. However, it was of considerable interest to study the cardiovascular system of these patients, in order to determine whether or not there was evidence of any disturbance in spite of the lack of symptoms referable to the heart.

Cardiac Signs.—The heart rate was found to be lower than in the former group, the average being 75 beats per minute. The heart was enlarged in three patients. In one of these, the blood pressure was low, and there was a systolic murmur over the mitral and pulmonary areas. In the others, the heart was of normal size and there were neither murmurs nor any other signs of changes in the cardiovascular system.

The blood pressure was practically the same in this group as in the former; namely, in some it was normal, in others either elevated or below normal.

Electrocardiographic Examination.—The electrocardiograms were essentially the same as those of the group with cardiac insufficiency. The observations are summarized briefly in table 3. The rhythm was always regular. Right ventricular preponderance was present in three patients, and left ventricular preponderance in two. The voltage was low in five and the P-R interval was lengthened to 0.2 second in two. The T wave was negative in leads 1 and 2 in one case and negative in lead 3 in two. The T wave was also high in lead 2 in three cases.

It may be seen, therefore, that in spite of the absence of symptoms of cardiac insufficiency minor electrocardiographic changes were present, indicating that the myocardium was involved before symptoms of insufficiency appeared.

Roentgen Examination of Heart.—The results of the roentgen examinations in this group of patients are recorded in table 4. Two of the patients showed definite cardiac enlargement. The type of enlargement was the same as that in the former group.

Neurologic Examination.—In the discussion of the patients with heart failure, it was stated that the neurologic disturbances were

are transmitted through the rod. The rod is then turned so that the bent point is passed toward either the right or the left coronary orifice. This is more easily accomplished for the left than for the right orifice, and requires considerable practice.

Dog 500.—The carotid artery was dissected out and freed from surrounding structures, under local anesthesia, and the brass rod introduced as described. This was the first experiment of this series.

During manipulation of the rod a point was found which produced pain. On removal of the rod from this point, the pain immediately disappeared. The point was found again and the wire held firmly in place. This was done with a fear that the movement of the animal would dislodge the rod. Instead, the briefest moment of pain, dyspnea and rapid irregular pulse was followed by instantaneous death. This spectacular result precluded minute observation of events leading to death.

Careful dissection while the rod was held in place revealed the tip of the rod completely occluding the left coronary artery.

Dog 501.—After several failures to find the coronary, the technic was developed to a point where by measurements and the "feel of the rod" the orifices could be found with a large percentage of success.

In this dog, on passing the wire into the artery, an obstruction was felt, which was judged to be the left coronary orifice. Preceded by a moment of struggle and pain, death occurred suddenly. The movements dislodged the point in the orifice. The momentary occlusion apparently produced a cardiac damage from which the animal could not recover, possibly a ventricular fibrillation. When the chest was opened the auricles and ventricles were fibrillating.

By direct observation, the rod held in the same manner readily entered the orifice of the left coronary artery.

Dog 502.—The animal was prepared as in the second preceding case (dog 500). In this animal repeated touching of two points presumed to be the right and left coronary orifices produced pain, dyspnea and rapid irregular pulse. Apparently neither orifice was occluded sufficiently to cause death.

Under ether anesthesia the heart was exposed and the rod repeatedly passed to both coronary orifices by the same manipulations as those causing pain.

Dog 503.—The animal was prepared in the same way as dog 500. The rod was passed to a point in the aorta which produced pain, dyspnea and a rapid irregular pulse. The rod passed easily for an inch and one-half further. This animal was immediately killed by injection of ether intravenously.

The rod, which was smaller than the usual one, was found to have passed into the left coronary artery and down to the circumflex branch to the point of the curve downward over the ventricle (fig. 6).

Dog 504.—The dog was prepared as dog 500. In this experiment the tip of the rod was wound with cotton to form a small ball for complete closure of the orifice of the coronary. During manipulation the animal suddenly died in the same manner as dog 500.

Immediate examination revealed a long thrombus which had gathered about the cotton. One-half inch of this thrombus extended into the left coronary artery, completely occluding it.

Dog 302.—The animal was prepared as dog 500. The blood pressure was taken by inserting a cannula into the right femoral artery (under local anesthesia)

TABLE 3.—*Electrocardiograms of Patients with Beriberi Without Signs of Cardiac Insufficiency*

No.	Heart Rate per Minute	Rhythm	P-R Interval, Seconds	Diagnosis	Remarks
1	100	Sino-auricular	0.16	Normal mechanism	
2	75	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	Low voltage in lead 1
3	55	Sino-auricular	0.16	Normal mechanism	Low voltage in all leads; T ₂ and T ₃ negative
	60	Sino-auricular	0.16	Normal mechanism	Negative
4	110	Sino-auricular	0.14	Normal mechanism; left ventricular preponderance	P wave and T wave negative in lead 3
5	50	Sino-auricular	0.14	Sinus bradycardia	
6	84	Sino-auricular	0.18	Normal mechanism	Low voltage in lead 1; high T ₂
7	80	Sino-auricular	0.16	Normal mechanism; left ventricular preponderance	T ₃ negative
8	76	Sino-auricular	0.16	Normal mechanism	Low voltage in lead 1
9	90	Sino-auricular	0.16	Normal mechanism; right ventricular preponderance	Low voltage in all leads
10	65	Sino-auricular	0.20	Normal mechanism; sinus arrhythmia	T ₂ high
11	86	Sino-auricular	0.15	Normal mechanism	T ₁ negative
	99	Sino-auricular	0.15	Normal mechanism	T ₁ iso-electric
	95	Sino-auricular	0.14	Normal mechanism	T ₁ positive; T ₂ -T ₃ high
12	65	Sino-auricular	0.20	Normal mechanism	T ₃ negative
12a	60	Sino-auricular	0.18	Normal mechanism	T ₂ high

TABLE 4.—*Results of the Roentgen Examination of the Heart in Patients with Beriberi Without Signs of Cardiac Insufficiency*

Pa-	Day of Observation	Diaphragm			Transverse Diameter, Cm.			Surface Area of Heart			
		Motility (Fluoroscopic Examination)	Position		To Right of Midsternal Line	To Left of Midsternal Line	Total	Estimated Normal, Sq. Cm.	Measured Areas, Sq. Cm.	Oversize, Sq. Cm.	Aorta, Cm.
			Right	Left							
1	1st	Movement normal	10th rib	11th rib	5.5	9.7	15.2	103.48	148.0	45.4	6.6
	5th	Movement normal	10th rib	11th rib	4.8	8.9	13.7	103.48	121.3	17.8	6.4
	15th	Movement normal	10th rib	11th rib	4.2	7.6	11.8	102.80	92.9	10.0	6.5
2	1st	Movement normal	10th rib	10th rib	5.0	9.5	14.5	96.18	134.5	38.0	4.7
3	1st	Movement normal	10th rib	11th rib	4.3	8.7	13.0	102.61	107.9	5.3	4.7
4	1st	Movement normal	10th rib	10th rib	3.3	8.1	11.4	94.33	89.0	5.0 (under size)	4.3
5	1st	Movement normal	10th rib	11th rib	5.0	7.8	12.8	5.2
6	1st	Movement normal	10th rib	9th rib	3.2	8.6	11.8				
7	1st	Movement normal	10th rib	11th rib	4.0	7.0	11.0				
	11th	Movement normal	10th rib	10th rib	3.5	7.0	10.5				
8	1st	Movement normal	10th rib	10th rib	3.0	8.1	11.1				

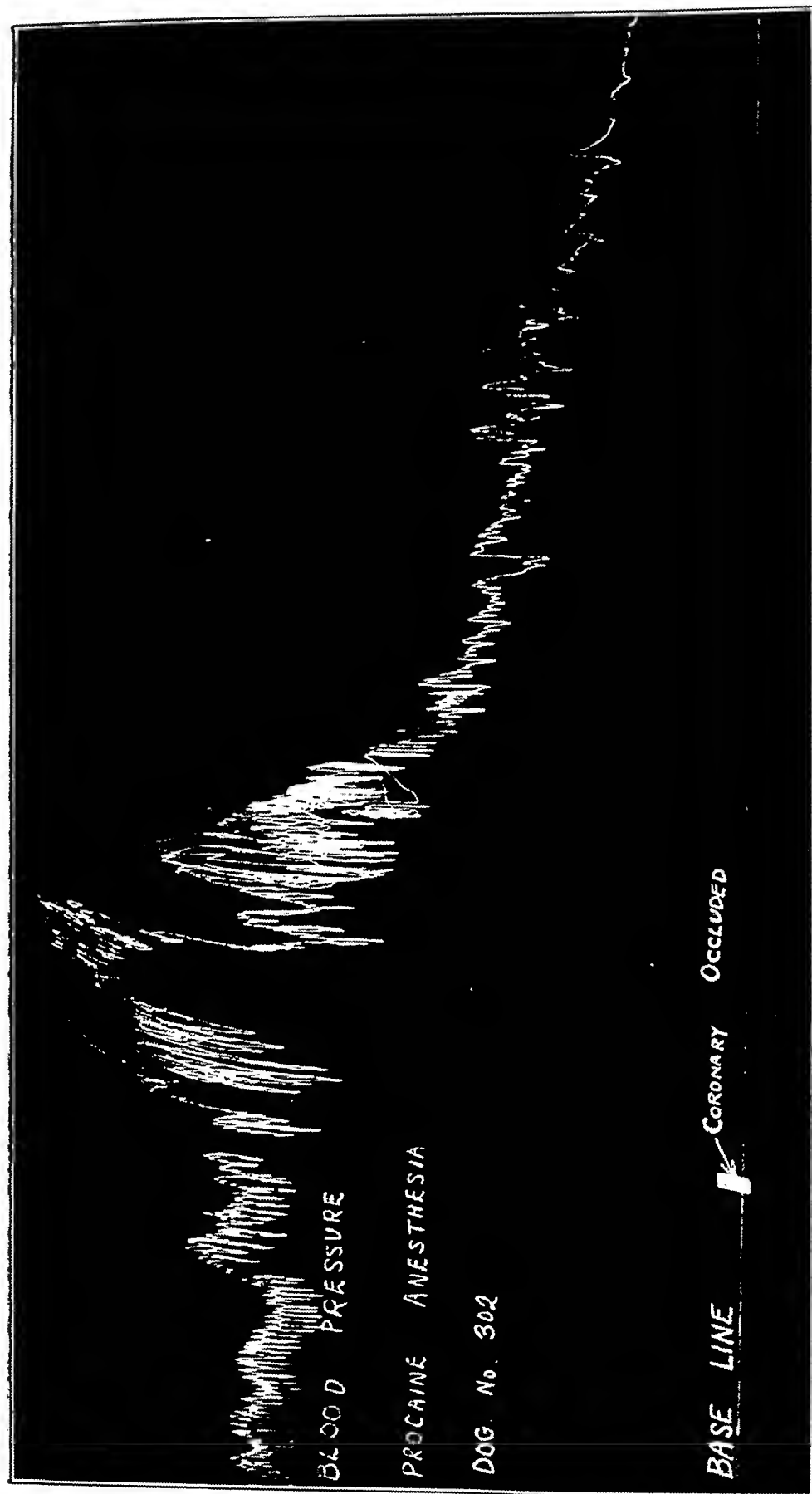


Fig. 7.—Blood pressure tracing in dog 302 taken at the time of occlusion of the coronary artery through the carotid artery, showing the effects of sudden complete occlusion of the left coronary artery on respiration and blood pressure.

comparatively mild except in the two fatal cases. In this group, the neurologic disturbances predominated. The observations have been tabulated in table 5. It may be readily observed that in the patients without heart failure, both the motor and the sensory disturbances were marked. None of them had normal muscular power in the legs, five had diminished muscular power and seven were completely paralyzed. The three patients with enlarged hearts had only diminished muscular power, and were still able to walk with some assistance.

None of the others had cardiac enlargement. On the other hand, in the group with heart failure, ten patients had normal muscular power in the legs, four had diminished muscular power and only one had complete loss of muscular power. The sensory changes were mild.

The case to be reported illustrates the changes that may occur without heart failure.

TABLE 5.—*Neurologic Disturbances in Patients with Beriberi*

Groups Studied	Total Num- ber of Cases	Loss of Knee Kicks and Ankle Jerks	Nor- mal Mus- cular Power	Dimin- ished Mus- cular Power	Par- aly- sis of Legs	Sensory Conditions				
						Nor- mal	Sense of Touch Absent	Sense of Vibra- tion Absent	Sense of Pain Absent	Sense of Tem- perature Absent
Patients with heart failure.....	15	15	10	4	1	12	3	1	0	0
Patients without heart failure.....	12	12	0	5	7	2	10	6	5	5

REPORT OF CASE

CASE 4.—*History*.—A Chinaman, aged 27, entered the hospital complaining of a slight edema of the extremities, of four months' duration, and weakness of the legs, of six weeks' duration. For the past four years, he had lived on a diet that consisted principally of rice and wheat. He seldom ate meat and on rare occasions had vegetables with his meals.

For several months he had noticed swelling of his legs, and slight puffiness about the eyes in the morning. For one month before admission he had noticed progressive weakness of both legs, and this had increased until he was able to stand or walk only when assisted. He had also had some numbness and tingling of the lower extremities, and some pain in his legs, especially on pressure. He had never had shortness of breath or palpitation. It is important to note that his disability was due to weakness of the legs and inability to walk.

Examination.—On examination, he appeared comfortable at rest. He could stand on his feet only with assistance. There were no signs of congestive heart failure, and no dyspnea, orthopnea or cyanosis. The cervical veins were not engorged, and the lungs were normal. The apex beat of the heart was 11 cm. from the midsternal line, and the impulse was diffuse. There were no thrills. The heart was enlarged. The cardiac dulness extended 11 cm. to the left of the midsternal line in the fifth intercostal space, and 4 cm. to the right of the midsternal line in the fourth intercostal space. The rate was 90 per minute and the rhythm regular. At the apex there was a soft systolic murmur, and over the

this manner, the muscle and visceral pericardium have been torn at the following points: (1) through the apex of the left ventricle; (2) through the aorta at the aortic cusp and on through the left auricle; (3) through the interventricular septum and out through the anterior or lateral wall of the right ventricle; (4) in one instance, through the aorta and then through the left auricle.

In no instance was definite pain noted. Hemorrhage into the pericardial cavity produced, however, marked restlessness and dyspnea.

In dogs 204, 205 and 206, 80 per cent alcohol was injected subpericardially without pain. The points of these injections were on both

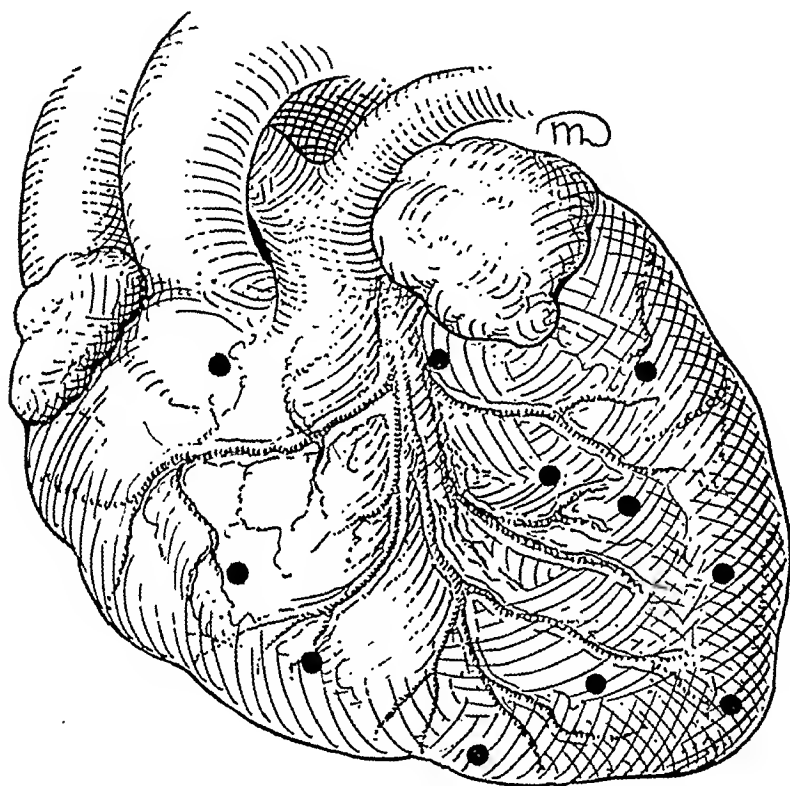


Fig. 8.—Diagram of heart; the black areas show points of mechanical and chemical stimulation of the visceral pericardium and myocardium.

sides of the ramus descendens anterior sinister. In no instance was pain produced.

Ammonium hydroxide, 5 and 10 per cent, was injected subpericardially into dogs 202 and 203, in about the same location as the alcohol. No pain was noted.

Into three dogs barium chloride (1 per cent and 5 per cent solutions) was injected through the cocainized wall of the chest into the apex and anterior aspect of the left ventricle. At postmortem examination in each instance an area of ischemia and localized retraction was found, the largest being 1 cm. in diameter. No pain was observed in this group.

In two dogs, 0.5 cc. of fluid extract ergotamine was injected through local anesthesia of the wall of the chest into the apex of the left ventricle. This produced no pain.

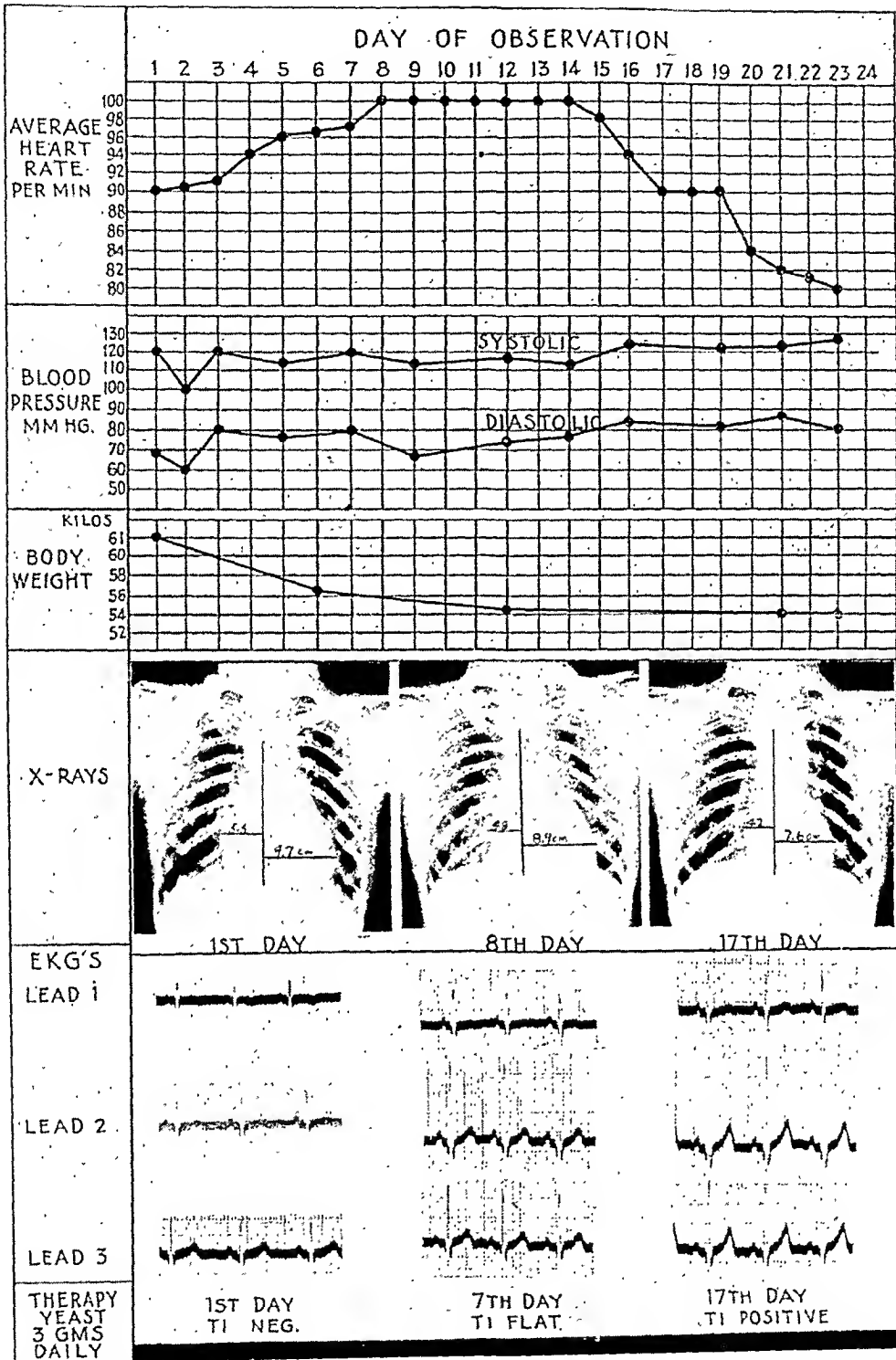


Chart 4. (case 4).—Observations in a case of beriberi without cardiac insufficiency. The treatment consisted of rest in bed and an adequate diet.

Without denying the possibility of the existence of such a condition as vascular spasm, its presence is not necessary to explain anginal pain. For example, in the cardiac sensations of "second wind," or on exertion in the patient with cardiac disease, the sensations may be due to a failure of the coronary arteries to dilate and so supply the heart with an extra supply of nourishment to care for the extra work it is called on to perform. On this principle, drugs act beneficially in such cases by causing adequate dilatation to meet the demand of the cardiac muscle for proper nourishment. Under normal physiologic conditions, the coronary arteries are able to respond adequately up to the point of extreme exertion, or "second wind," when other extra compensatory factors enter in; but in the patient with angina, the coronary dilator mechanism fails to operate, and dilator drugs become necessary.

On the other hand, a large percentage of persons with most marked sclerotic changes have never suffered from angina pectoris. Variations in the increasing anastomosis of the coronary arteries that results with increase in age, as shown by Gross,⁸ may well be the deciding factor. These variations in anastomosis offer an explanation for the absence of pain in cases of advanced coronary sclerosis. This offers an explanation for the rarity of nonsyphilitic angina pectoris in clinics attended largely by laborers. As a result of life-long strenuous exercise, a much more free anastomosis of the coronary arteries and a more responsive dilator mechanism might be expected in laborers than in those of more sedentary habits.

Experimentally, temporary occlusion of the coronary arteries has caused temporary pain, whereas permanent complete occlusion does not lead to permanent objective manifestations of pain in dogs; the sudden decrease in blood supply apparently causes the pain. The pain has persisted as long as compression has been continued in conscious animals, but is not evident after the animal with a permanent obstruction of the coronary artery has recovered from the anesthesia. The duration of the pain of permanent occlusion is less than the period required for recovery from ether anesthesia, and greater than even a ten minute temporary occlusion. If a limp in the left foreleg is accepted as evidence of pain, the persistence of pain after recovery from anesthesia has been observed.

This is at variance with the clinical presence of pain in cases of coronary thrombosis in which the pain may last from hours to days, unless a slowly forming retrograde thrombus with closure of additional small branches causing gradual increase in the ischemic area is the cause of prolonged pain. This is in accordance with conditions observed anatomically in cases exhibiting pain of long duration ending in death.

8. Gross, L.: *The Blood Supply to the Heart*, New York, Paul B. Hoeber, Inc., 1921.

pulmonary area a loud systolic murmur followed by a loud accentuated second sound. The blood pressure was normal, and there was no capillary pulsation or increased sounds over the peripheral arteries.

Examination of the nervous system revealed marked diminution of the muscular power in the legs, particularly in the anterior tibial muscles. There was no atrophy. The deep reflexes were absent. Plantar response was normal. There was hypesthesia to touch from the middle of the thigh downward. The sense of vibration was lost over the legs, and there was a diminution of the pain sense.

There was no anemia. The urine was clear and the excretion of phenolsulphonphthalein was 45 per cent in two hours. The Wassermann reaction was positive. The ocular fundi were normal. The results of the electrocardiographic and roentgen examinations are recorded in chart 4.

The patient's clinical course can be followed from chart 4. With rest in bed and 3 Gm. of yeast daily, the heart decreased in size, the heart rate gradually fell and the patient's general condition improved. He regained some of his muscular power and was able to walk, but the deep reflexes did not return while he was under observation.

Summary.—A man with signs of an extensive polyneuritis and inability to walk, had cardiac enlargement without symptoms or signs of cardiac insufficiency. This illustrates the fact that the heart may be involved in patients with beriberi, even though they do not have symptoms or signs of heart failure.

The only way in which this patient differed from those with heart failure was in the absence of signs of congestive heart failure and the presence of signs of an extensive polyneuritis. The same type of cardiac enlargement and electrocardiographic changes were present, but other signs failed. It is highly probable that myocardial failure would have appeared if the patient had been capable of carrying on normal activities.

COMMENT

It seems apparent from the cases described that the patients who have heart failure in beriberi are those who have mild neurologic signs and a preservation of muscular power. If they are able to carry on normal activities, a burden is placed on the heart, which is already embarrassed by the deficiency of vitamin. This causes a failure of the myocardium. If the nervous system is extensively involved, so that a polyneuritis develops, the patient is unable to carry on normal activities. As a result, the burden of exercise is not placed on the heart and failure does not occur.

It has been pointed out by Aalsmeer and Wenkebach¹⁵ and Stanley¹⁵ that heart failure may occur in patients with beriberi before neurologic signs appear. One also finds supporting evidence of this fact in the papers of Sprawson,¹⁶ Vitug¹⁷ and others. While the presence or

15. Stanley, A.: Beriberi and the Heart, *J. Trop. Med.* 4:351, 1901.

16. Sprawson, C. A.: The Heart in Beriberi and the Evidence of the Differential Stethoscope, *Indian J. M. Research* 9:625, 1921-1922.

17. Vitug, W.: Some Clinical Aspects of Acute Cardiac Beriberi in Adults, *J. Philippine Islands M. A.* 6:380, 1926.

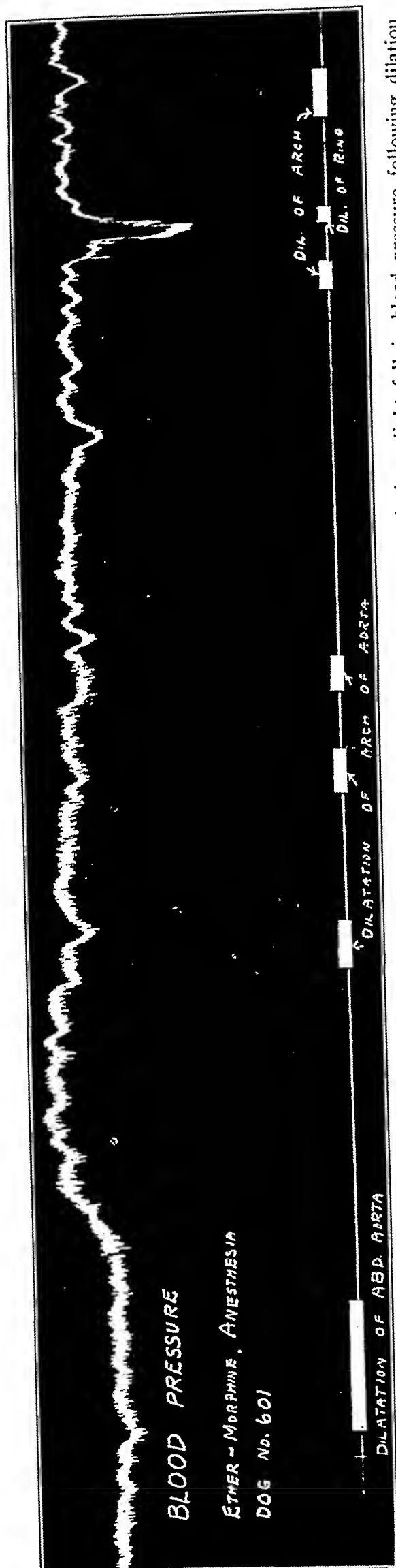


Fig. 11.—Curve for dog 601. Note lack of response during dilation of the abdominal aorta with delayed rise; slight fall in blood pressure following dilation of the arch of the aorta, and marked fall in blood pressure (66 mm. of mercury) during dilation of the aortic ring.

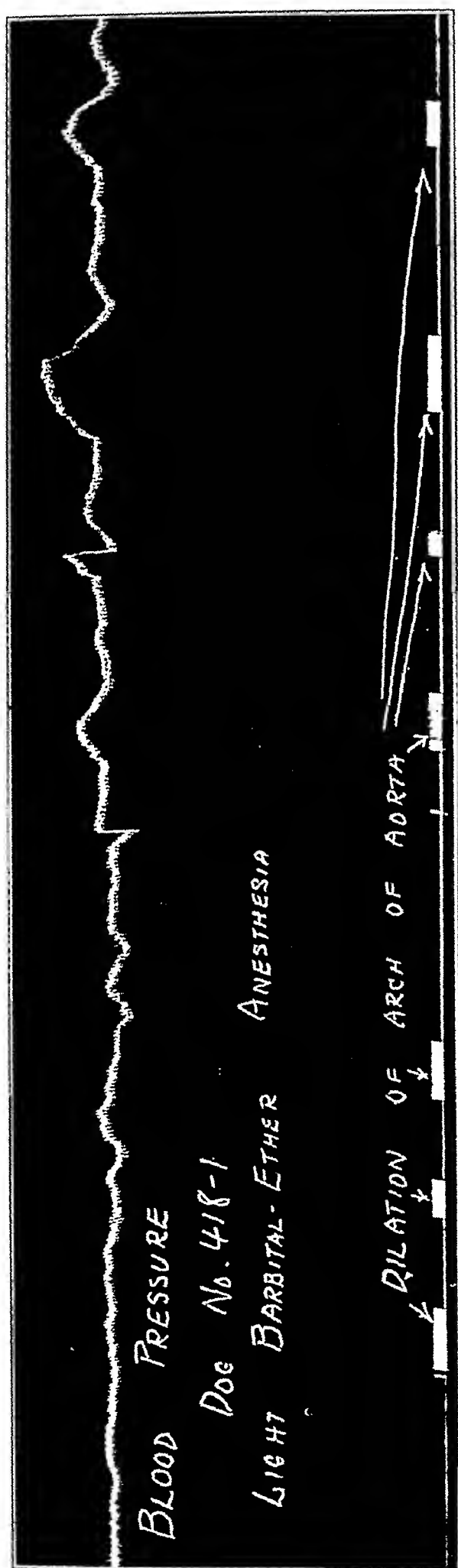


Fig. 15.—Curve for dog 418. Note increasing rise in blood pressure following repeated dilations of the arch of the aorta (highest, 30 mm. mercury).

posed by Aalsmeer and Wenkebach.⁸ These authors feel that a deficiency of vitamin B leads to a disturbance in metabolism which results in both the skeletal and heart muscles absorbing water. This absorption of water leads to edema of the heart muscle with a resulting disturbance in contractility and heart failure. Wenkebach pointed out that in beriberi there are swelling of the muscles, edema and a disturbance in contractility of the heart muscle, without disturbances in conductivity.

In order to account for the disturbances in contractility without disturbances in conductivity on the basis of edema of the heart muscle, they emphasized the fact that Englemann, De Boer and others have shown that when skeletal or heart muscle absorbs water under experimental conditions, disturbances in contractility result, while conductivity remains normal. Since similar changes occur in the heart in beriberi, and since edema of the muscles is a prominent feature of this disease, they concluded that the fundamental cardiac disturbance is due to absorption of water by the heart muscle.²⁰

Wenkebach explained the enlargement of the right side of the heart in the following way. He felt that at the beginning of the illness both sides of the heart are involved equally, but, in any case, when the whole heart fails, the right side is doomed before the left. He explained this, first, by the anatomic difference in the two sides of the heart, the right being weaker than the left, and secondly, by the fact that the right side of the heart must deal with all the blood that returns from the periphery, whereas the left side does not receive more blood than the right side is able to transmit. As a result, the right side is struggling against a greater burden than the left. The more the right side of the heart suffers the better the left becomes, since in myocardial insufficiency the blood finally gets to the right side of the heart, but is only partially transmitted to the left, thus reducing the burden of the left chambers.

Furthermore, he concluded that the latter explanation accounts for the signs seen in beriberi, namely, struggle of the right side of the heart, clear lung fields as shown by x-ray pictures and a small rapid pulse indicating competence of the left ventricle.

20. Since this paper was written, I have learned of some recent, as yet unpublished, observations which seem to support the view that edema is an important cause of the heart failure of beriberi. Harrison and Pilcher (personal communication to the author) found that edema of the tissues causes increased local blood flow, which would tend to increase the work of the heart. The same authors also found that edema causes a diminution in the buffering power of the tissues, and they believe that this effect may be the physicochemical basis for cardiac "fatigue." From their work it appears that edema, originally an effect of congestive failure, is secondarily a cause of further heart failure. The application of their observations to the condition of the heart in beriberi is obvious. The clinical observations reported in this paper seem both to confirm and be confirmed by the experimental observations of Harrison and Pilcher.

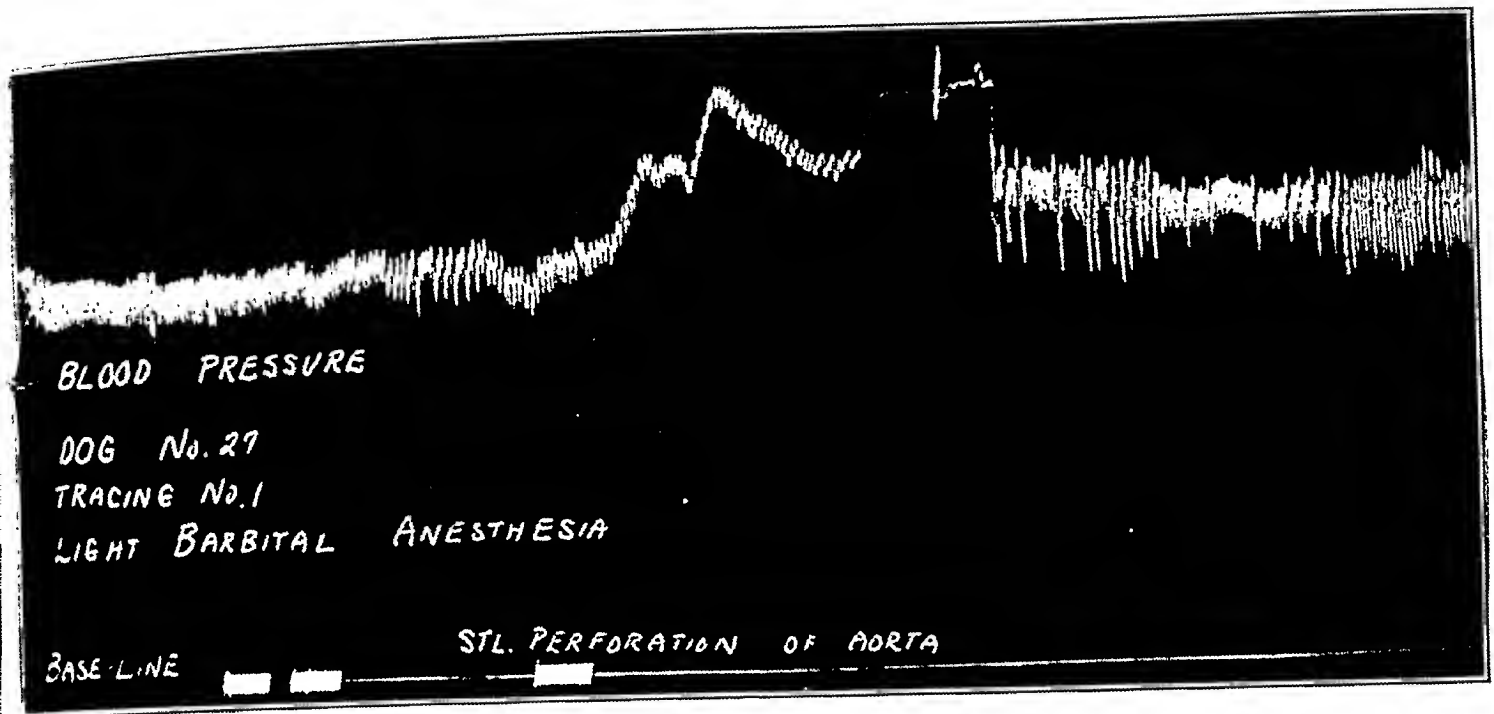


Fig. 17.—Curve for dog 27, showing effect of slight perforation of the aorta on blood pressure.

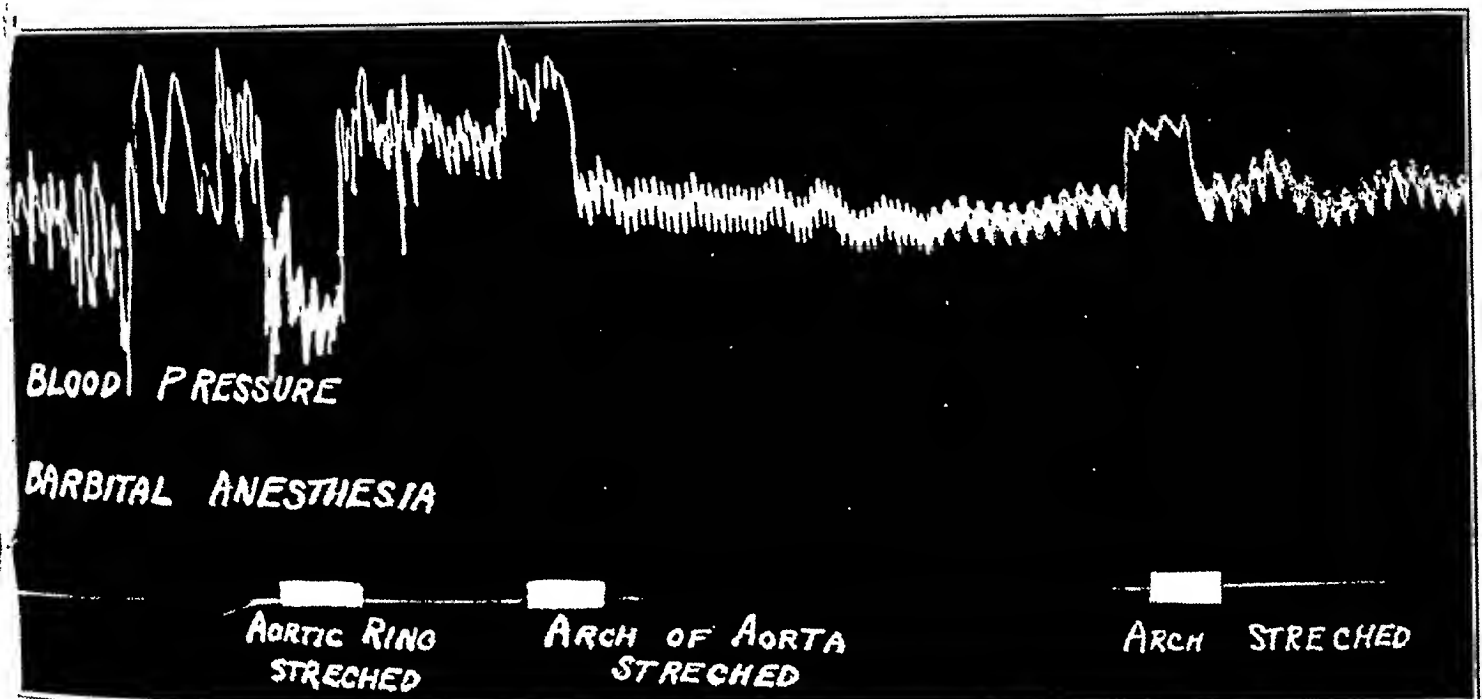


Fig. 18.—Curve for dog 430. Note prompt fall in blood pressure on stretching aortic ring and prompt return to normal following release of pressure. Note prompt rise in blood pressure when arch is stretched and also prompt fall on release of pressure.

Mebius²¹ supported the edema hypothesis and went even further. He was of the opinion that a deficiency of vitamin B produces a disturbance in the osmotic pressure of the anisotropic contractile substance of the heart muscle, and that this leads to cardiac weakness. He supported this hypothesis by recording his observations in the hearts of three patients dying of beriberi. The longitudinal striations of the heart muscle were distinct, whereas the cross striations were indistinct and there was an intercellular edema. He compared these observations with the changes that occur in a strip of muscle when it is allowed to absorb water. In support of the argument that these changes are not due to degeneration of the nerves, he stated that many cases of beriberi in the acute stage do not show degeneration of the nerves at necropsy. One may summarize the edema hypothesis by saying that the fundamental disturbance in beriberi is due to absorption of water by the heart muscle, causing defective contractility and heart failure.

On the whole, this explanation of the cardiac disturbance in beriberi seems reasonable. How, then, does muscular exercise exaggerate this condition? This problem has been studied recently by Inawashiro and Haynasaka,²² who found that patients with beriberi have an increased circulatory minute volume, an increased amount of lactic acid in the blood, and a diminished carbon dioxide content of the venous blood while they are at rest. Following muscular exercise, there is a further increase in the circulatory minute volume, and in the amount of lactic acid in the blood, a further decrease in the carbon dioxide content of the venous blood and an increase in the systolic, and a decrease in the diastolic, blood pressure. They concluded from their observations that the fundamental factor in vitamin B deficiency is a disturbance in muscle metabolism with a resulting acidosis, and that this disturbance is exaggerated by muscular exercise. They were of the opinion that the increased circulatory minute volume together with the paralysis of the respiratory muscles and the acidosis, accounted for the enlargement of the right side of the heart. They attributed the increased circulatory minute volume to a relaxation of the peripheral vessels, due in part to vasomotor paralysis and in part to acidosis.

In summarizing the observations on the mechanism of cardiac insufficiency in beriberi, it might be said that a deficiency in vitamin B causes changes in the heart muscle. These changes are characterized by cardiac enlargement and deficient contractile power. The conductivity is altered slightly in some cases, but as a rule it remains normal.

21. Mebius, J.: Oedemtheorie der Beriberi und physiologische Wirkung des Vitamine B, *Virchows Arch. f. path. Anat.* **271**:422, 1929.

22. Inawashiro and Hayasaka: *Tohoku J. Exper. Med.* **12**:1 (Dec. 30) 1928.

by cannula in the left femoral artery. Stretching of the ascending portion and arch produced no change in blood pressure. After section of the vagi, no changes in blood pressure followed when the aorta was stretched, and a fall (30 mm. of mercury) occurred when the ring was stretched.

Dog 430.—With the animal under barbital anesthesia the left carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded from the right carotid artery. Stretching of the ascending portion of the aorta produced a prompt rise in blood pressure of 26 mm. of mercury, with a prompt fall on release of pressure. Stretching the aortic ring caused a fall of 80 mm. of mercury (fig. 18).

Dog 60.—With the dog under barbital anesthesia, this animal was prepared as was dog 601. When the dilator was passed into the cavity of the left ventricle, one of the springs broke. Attempts to withdraw the instrument resulted in its becoming entangled with the chordae tendineae of the mitral valve. The marked effect on blood pressure resulting when traction was made on the chordae tendineae is shown in figure 19. The sympathetic was cut, following which traction was again made with a fall of blood pressure which persisted, causing the death of the animal.

SUMMARY

Effects of Stretching the Aorta, Aortic Ring and Ventricular Cavity on Pain and Respiration.—It is found that pain is not produced (1) by insertion of an instrument into and stretching of the carotid artery; (2) by sufficient pressure to pierce the aortic wall when obstruction is met at the junction of the carotid and aorta; (3) by passing the instrument into the ascending aorta and stretching it sufficiently to cut the intima; (4) by passing the instrument into the aortic ring, and (5) by perforation of the aorta, which has occurred a number of times from the breaking of the dilator spring; it does not result in pain until a sufficient quantity of blood has collected in the mediastinum to produce much stretching of the limiting tissues.

It is found that dyspnea follows stretching of the ascending aorta, aortic ring and left ventricle. This dyspnea is variable in degree, depending on the amount of stretching.

Effects on Blood Pressure of Stretching the Aorta, the Aortic Ring and the Ventricle (Preliminary Observations).—The universal acceptance of a depressor nerve would lead one to expect a fall in blood pressure when the aortic ring, ascending aorta or arch are dilated. Because of the finding of an isolated depressor nerve in rabbits, it has been presumed that depressor fibers are present in the vagus in all higher forms of animal life, including man. In no instance has dilatation of the ascending aorta produced a definite fall of blood pressure that would indicate the stimulation of a depressor nerve. On the other hand, in two cases (dogs 418 and 430) there was an immediate definite rise in blood pressure (26 mm. of mercury) which lasted during the period of stretching and promptly returned to normal on release of

Muscular exercise plays a tremendous rôle in the course of the disease. If the patient is not disabled by polyneuritis and performs muscular work, cardiac insufficiency results. If polyneuritis is present, the myocardium is usually protected from the increased burden of muscular exercise, and cardiac failure does not appear.

This type of heart failure emphasizes two points of importance in the study of any form of heart disease, namely, the rôle of nutrition and the rôle of exercise.

Recently Smith²³ emphasized the importance of a proper diet in the treatment of heart disease. The results he obtained following the treatment of patients with heart failure with diets of high carbohydrate value are suggestive that a proper dietary regimen plays a part in the recovery of many. Certainly in the form of heart failure under discussion a proper diet is absolutely essential for recovery. This is well illustrated by the patients in whom prompt recovery took place following the administration of an adequate diet and yeast without the giving of digitalis.

The rôle of muscular exercise in the production of any form of heart failure is of importance. This subject was recently reviewed by Barr.²⁴ He emphasized the importance of muscular exertion in producing conditions which result in the symptoms and signs of heart failure. In no type of heart disease is this fact better illustrated than in the cases described. If the patient is unable to carry on exercise owing to peripheral neuritis, cardiac insufficiency does not appear.

SUMMARY

A group of patients with beriberi were studied with particular reference to the cardiovascular system. It was clearly demonstrated that the patients who develop cardiac insufficiency are those who have the least involvement of the nervous system. The hypotheses that have been advanced in explanation of the mechanism of heart failure in this disease were reviewed and the mechanism discussed. The importance of diet and exercise in the management of heart disease was emphasized.

23. Smith, F.: Diet and Theophylline in Cardiac Failure, *J. A. M. A.* **91**: 1274 (Oct. 27) 1928.

24. Barr, D. P.: Exercise in Cardiac Disease, *J. A. M. A.* **91**:1354 (Nov. 3) 1928.

esses. It is generally believed that even small areas of cardiac disease in this area may give graphic evidence of a delayed QRS interval; widespread damage must be produced, however, in the region involving the left main bundle before there is evidence of this condition.

Recently, Luten and Grove¹² studied the development of bundle branch block from its beginning; in a series of 237 cases showing left axial deviation of the heart with altered T waves in the first lead, subsequent evidences of right bundle branch block were shown. They expressed the belief that the condition is closely associated with hypertensive heart disease with accompanying myosclerotic changes.

Reviewing carefully cases showing a left axial deviation of the heart, we have selected a group with tracings having the characteristic QRS and T wave positions of right bundle branch block but without the QRS delay. In other words, of a group of 469 cases showing left axial deviation of the heart we have picked 46 that show an upright QRS and a negative T wave in the first lead and a downward QRS and an upright T wave in the third lead. These cases have been followed for periods ranging from eight months to four years. Of the 46, 21 developed true right bundle branch block with no change of sinus rhythm and 8, auricular fibrillation with bundle branch block; 4 showed complete auricular and ventricular dissociation with bundle branch block, and the remaining 13 showed right bundle branch block with an extrasystolic arrhythmia from single and multiple foci. In this connection, we have been able to watch one case of right axis deviation of the heart which developed into a true left bundle branch block prior to the death of the patient. This case is interesting in that it showed in every respect the reverse observations of those seen in the other group of cases.

We have selected one case from each of the four types mentioned in right bundle branch block.

REPORT OF CASES

CASE 1.—A widower, aged 56, a laborer, had a long history of hypertensive heart disease. At the age of 40 he was rejected for life insurance; at 51 he was known to have a blood pressure of 210 systolic and 105 diastolic. Three years later, he began to have symptoms of dyspnea, palpitation and substernal distress even on mild effort. Electrocardiographic studies made at that time (fig. 1A) showed a left axial deviation of the heart with a QRS complex measuring 0.08 second: T1 was diphasic. Physical examination revealed a heart that was not very large in spite of his long history of hypertension. The patient was seen again fifteen months later (fig. 1B), and the electrocardiogram was unchanged except for a slight slurring in the second limb of the QRS complex. The T wave seemed to be more inverted and less diphasic than before. A third examination was made about ten months later (fig. 1C); at this time, there was well marked

12. Luten, D., and Grove, E.: *Am. Heart J.* 4:431 (April) 1929.

CHRONIC GLOMERULONEPHRITIS WITH LIPOID CHANGES

A REPORT OF AN ILLUSTRATIVE CASE STUDIED FROM THE ONSET UNTIL DEATH FIVE YEARS LATER *

FRANCIS D. MURPHY, M.D.

MILWAUKEE

The clinical and morphologic features of chronic glomerulonephritis with lipoid changes are fairly well known. Often, however, such patients are studied for a short time only and during one period of the disease, usually at an advanced stage, when there are unmistakable evidences of well developed renal failure. There is, as a result, a disconnected clinical picture and a lack of appreciation of the proper sequence of events. The continuous study of a patient over a longer time usually furnishes some information that would be impossible to gather from shorter periods of observation. The illustrative case presented here was studied from the onset of the illness until death five years later. My object in this paper is to analyze the following features illustrated by the study of this case:

1. The major clinical syndromes are discussed; and it is shown that not all appear at the same time, but come and go with great irregularity. Some syndromes develop and dominate the clinical picture for a while and then fade away, either to return at a later date or never to return.

2. Hypercholesterolemia is considered, and its relationship to lipoid deposits in the kidneys and to arteriosclerosis is emphasized.

3. The changes found in the arteries and arterioles of the internal organs and skeletal muscles are described, and especial attention is given to changes in the arterioles of the kidney.

REPORT OF CASE

History.—A white boy, aged 12 years, was first taken sick in January, 1924. There was no history of any infectious diseases of childhood. He had had tonsillitis, and the tonsils were removed when he was 7 years old. The present illness began with a moderate generalized edema, vomiting and headache. The urinalysis revealed a mild albuminuria with few cellular elements. The blood pressure was normal; no other tests were done at that time. The edema disappeared rapidly, and within a week he felt fairly well. On March 9, 1924, after his mother died, he was admitted to the Milwaukee County Home for Dependent Children. On entrance the urine was free from albumin, and the blood pressure

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* From the Medical Clinic of the Milwaukee County Hospital and the Department of Medicine, Marquette University.

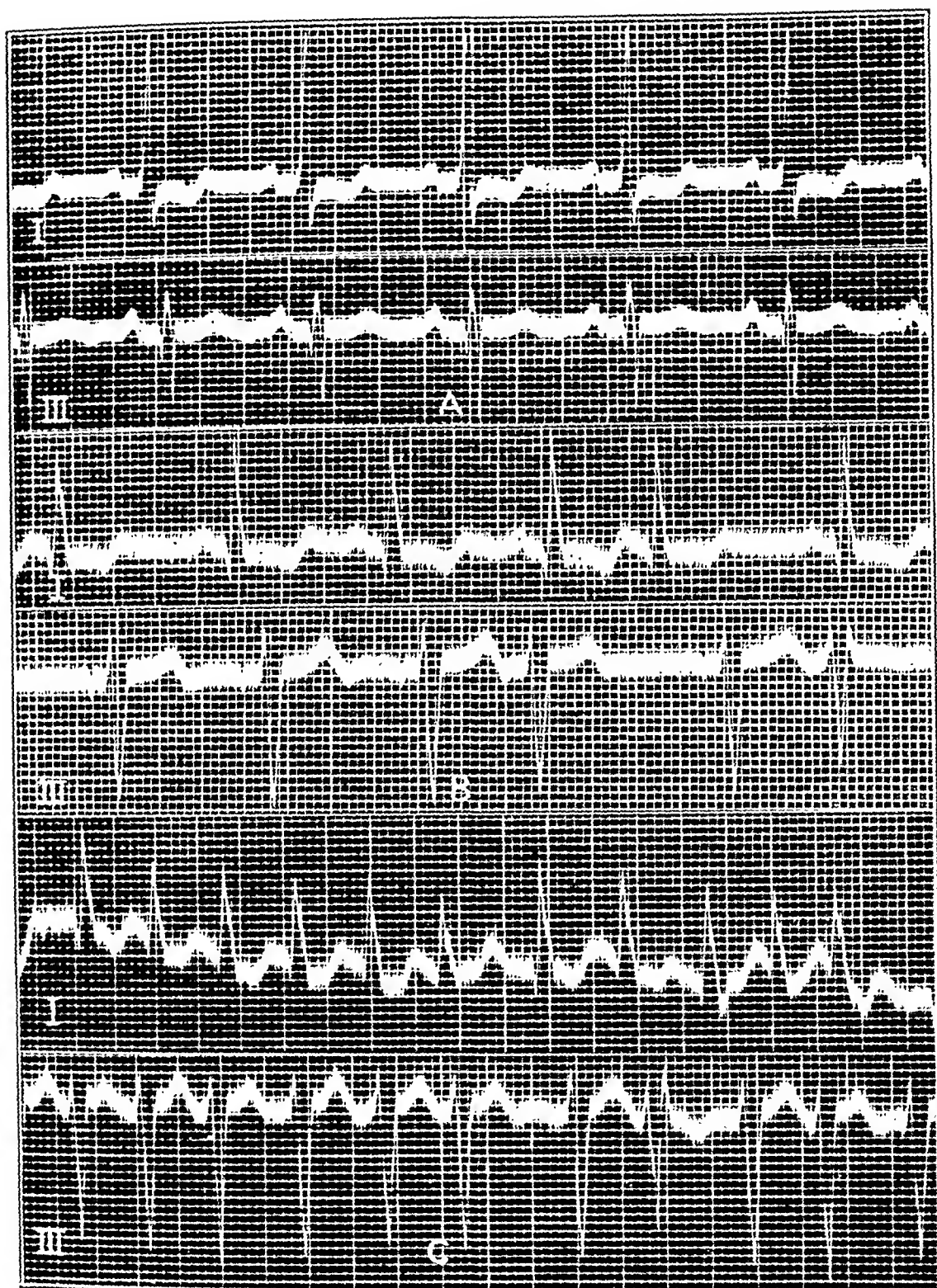


Fig. 2.—Development of auricular fibrillation with right bundle branch block twenty-six months after the appearance of left axis deviation.

was normal. He remained in good health until Nov. 6, 1925, when he was taken to the Milwaukee County Hospital because of cervical adenitis and generalized edema, most prominent about the face, as presented in the accompanying table.

At the examination on entrance to the hospital, the boy was well developed, with a butter-yellowish tinge to the skin. Urinalysis showed the albumin and cellular elements usually found in nephritis. A careful search for doubly refracting lipoids with the polarizing microscope revealed none. The chemical examination of the blood showed nothing abnormal, except for a well developed hypercholesterolemia. Renal functional tests disclosed normal results. The cardiovascular system was normal. There was a moderate secondary anemia. The eye grounds were normal.

Within a few weeks the edema and adenopathy had gone, and the patient felt well. The urine continued to have albumin in it, while the cellular elements gradually diminished until only a few cells and casts were found. The blood pressure remained normal; there was a slight improvement in the anemia, although the red cell count continued to be well under normal.

From the time of entrance to the hospital on Nov. 6, 1925, until Sept. 8, 1926, this patient was under continuous study. Renal function tests, blood counts, determinations of blood pressure and urinalyses were done as a routine.

Doubly refracting lipoids were sought for almost daily in the urine, and were first found on July 18, 1926. The cholesterol of the blood remained above 300 mg. per hundred cubic centimeters throughout the illness. The edema did not return until later in the course of the disease. The boy was dismissed from the hospital on Sept. 8, 1926, and sent back to school.

On Sept. 28, 1926, he developed a mastoid infection and came back to the hospital in a serious condition. He underwent a successful mastoid operation. During this crisis, the blood pressure remained normal, as did the blood nitrogen and other renal functional tests. The urine showed albumin 3 plus. Many hyaline and granular casts, red blood cells, pus cells and doubly refracting lipoids were also present. A profound anemia developed, the red cell count dropping to 1,600,000. No edema developed. Within a month after operation the blood count was 3,400,000, where it remained in spite of further treatment. The urine cleared up except for the presence of albumin 2 plus, a few cellular elements and many doubly refracting lipoids. On Dec. 10, 1926, the patient was dismissed from the hospital. In general, he appeared to be in good health and aside from the anemia, a mild albuminuria and a hypercholesterolemia, the examination and tests revealed no abnormalities.

During the early part of 1927, biweekly examinations were done in the outpatient department, and the boy appeared healthy and normal. The urine contained albumin and doubly refracting lipoids. The blood pressure remained normal; the hypercholesterolemia and anemia persisted. On or about April 1, a systolic murmur was heard for the first time over the aortic area. This murmur was transmitted down along the left sternal border and was heard distantly in the mitral area. Its quality was soft and not unlike a hemic murmur. During the remainder of the course of the disease, this murmur was studied. It became louder, but the area of transmission did not change.

In September, 1927, the boy was symptomless, although the blood pressure had risen (for the first time) to 148 systolic; 100, diastolic. The only other change found was a definite defect in the renal concentration ability, elicited by the dilution concentration test of Volhard. The MacLean urea concentration test also revealed evidences of the defect. He continued to go to school.

more serious light than a mere axis deviation of the heart. There is a growing tendency among cardiographers to consider a left axis deviation perfectly normal during and after the middle age period. When such axis deviation is associated with T wave changes in the first and third leads resembling the bundle branch block configurations, such cases must be regarded as potential types that may subsequently develop into true conduction disturbances of the most serious significance.

No discussion of etiology has been considered here, for it can be assumed that this process is one of advancing myosclerosis as a result

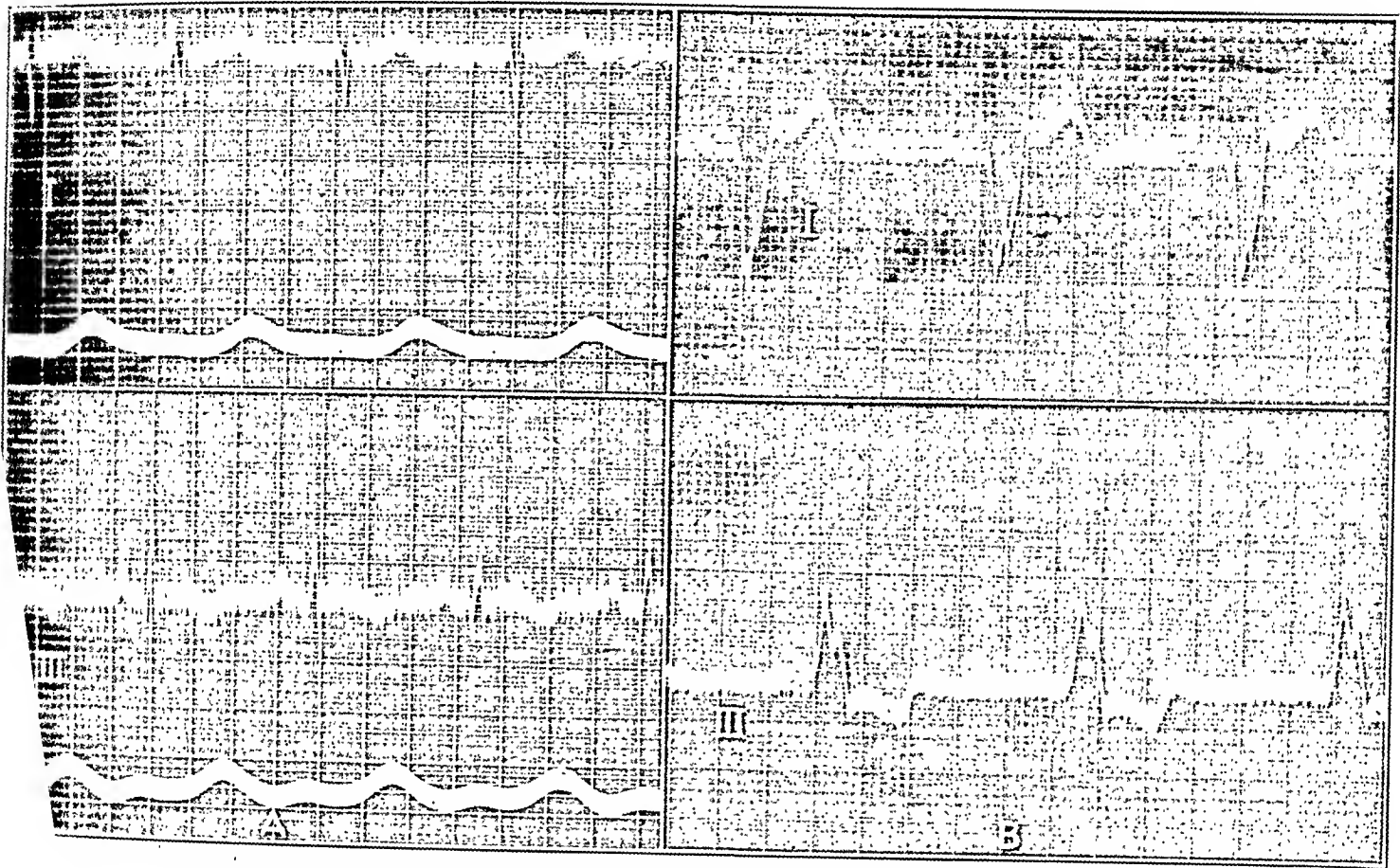


Fig. 5.—The development of a left bundle branch block from a previous right axis deviation, a relatively uncommon condition. Note that the tracings in lead I and IIIA show a moderate right axis deviation with T wave alterations in the third lead similar to that seen in the previous figures in lead I.

of heart muscle damage or disturbances in the coronary arterial circulation. While it is true that frequently cases presenting clinical evidence of coronary thrombosis may show left axial deviation of the heart with alterations of the T waves in the first lead which in many respects may be similar if not identical with those seen in the configuration discussed, T wave alteration of the purely coronary type is usually found in more than one lead. In fact, many observers believe that

Summary of Data in Case Report

Year	Urine							Blood Chemistry				Function			Comment			
	Albumin	Oliguria	Hyposthenuria	Red Blood Cells		White Blood Cells	Casts	Lipids, Doubly Refracting	Urea Nitrogen	Creatinine	Cholesterol	Carbon Dioxide Combining Power of Plasma	Red Blood Cell Count	Phenolphthalein		Dilution and Concentration Tests	Blood Pressure	Edema
3/16/24	2+	0	0	0	0	2+	0	115/80	2+	Eyegrounds normal
12/ 2/24	1+	0	0	0	0	0	0	110/70	0	
5/12/25	2+	0	0	0	0	0	0	115/80	0	Edema for 1 week
11/ 6/25	4+	2+	0	2+	2+	1+	Granular, 2+	0	14.9	2.0	327	..	3,500,000	70	1.004-1.026	118/70	4+	
12/31/25	1+	0	0	1+	1+	1+	Granular, 1+	0	11.2	1.6	390	65	1.002-1.022	110/65	0	Doubly refracting lipoids found for first time
4/ 4/26	3+	0	0	0	0	0	0	0	12.9	1.4	337	52	3,700,000	70	1.006-1.021	120/85	2+	
5/23/26	2+	0	0	1+	2+	2+	Granular, 1+	0	14.3	1.8	333	60	115/75	0	Dismissed from hospital
7/18/26	3+	0	0	0	1+	1+	Granular, 1+	2+	16.2	1.5	342	75	1.004-1.020	120/70	2+	
9/ 8/26	2+	0	0	0	0	1+	0	3+	15.1	1.3	361	..	3,800,000	65	115/60	0	Had mastoid operation
9/28/26	4+	2+	1+	3+	3+	3+	Granular and hyaline, 3+	4+	16.7	2.2	410	45	2,250,000	65	142/90	0	
12/10/26	2+	0	0	1+	1+	1+	0	4+	10.4	1.8	350	..	3,650,000	55	145/65	0	Edematous for 1 week
1/15/27	2+	0	0	1+	1+	1+	0	3+	15.3	2.1	347	58	65	130/80	0	
6/ 7/27	3+	0	0	1+	1+	1+	0	3+	16.2	1.3	325	..	3,800,000	55	1.006-1.022	125/170	3+	Developed bronchopneumonia
9/ 5/27	2+	0	0	0	2+	2+	0	3+	10.6	1.9	371	63	1.008-1.015	145/90	0	
11/11/27	3+	2+	2+	3+	3+	3+	Granular, 2+	4+	18.2	2.5	305	42	4,080,000	60	1.010-1.015	160/100	2+	Occasional headache only
12/ 2/27	3+	2+	3+	2+	2+	2+	Granular, 3+	3+	20.1	2.4	314	..	3,400,000	65	165/95	0	
12/23/27	3+	0	2+	1+	1+	1+	Granular, 1+	4+	12.6	1.2	309	50	1.005-1.012	150/100	0	Convulsive uremia; albuminuric retinitis when seen for first time
1/15/28	3+	0	2+	1+	1+	1+	Granular, 1+	3+	15.0	2.2	365	50	3,650,000	65	1.008-1.012	190/120	0	
2/ 2/28	3+	0	2+	2+	2+	2+	Granular, 2+	3+	17.4	2.0	322	70	230/150	1+	Appeared very well
3/15/28	1+	1+	2+	1+	0	0	0	3+	12.0	1.5	360	58	3,610,000	55	1.009-1.013	210/120	0	
5/ 2/28	1+	0	3+	2+	1+	1+	Granular, 1+	4+	20.2	2.6	315	40	1.008-1.012	200/125	0	Weak and felt poorly
8/21/28	3+	1+	3+	2+	2+	2+	Granular, 2+	3+	18.0	2.6	380	37	3,450,000	35	1.005-1.009	220/120	...	
11/ 7/28	3+	2+	3+	3+	3+	3+	Granular, 2+	4+	30.1	2.9	250	20	1.007-1.011	210/130	...	Stupor and twitching set in; died Dec. 20, 1928
12/15/28	3+	3+	3+	3+	3+	3+	Granular, 3+	4+	33.2	3.1	160	23	3,220,000	15	160/120	...	

The patient was placed in a room by herself, flat on her back on a Bradford frame. The patient and the nurse in charge were instructed that only the food given in the special diet was to be eaten by the patient, and that any food not eaten was to be weighed and noted by the dietitian. They were also informed that all excreta were to be saved for analysis.

Three diets, designated diet 1, diet 2 and diet 3, were used in the course of the metabolic studies. When it was desired to give more calcium or phosphorus than was provided for by the diet, calcium lactate and disodium acid phosphate were added to diet 2 or diet 3. Diet 1 (table 1), a neutral diet, low in calcium, and practically devoid of vitamins A and D, was given to the patient before medication was started, and at later times to learn the effect of treatment. Except for the low content of vitamin A and D, it was essentially like that given

TABLE 1.—*Diet 1. Low Vitamin, Low Calcium, Neutral Diet*

	Break- fast, Gm.	Din- ner, Gm.	Sup- per, Gm.	Total Gm.	Car- bohy- drate, Gm.	Pro- tein, Gm.	Fat, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.	Excess Acid, Cc., Normal	Excess Base, Cc., Normal
Bacon.....	15	15	3.45	10.05	0.004	0.014	1.78
Bread, low in calcium.....	50	50	50	150	79.80	12.00	3.15	0.017	0.121	11.83
Apple.....	100	...	100	200	27.00	0.60	1.00	0.020	0.036	7.52
Steak.....	...	75	...	75	15.95	6.00	0.006	0.129	9.60
Potato.....	...	100	150	250	45.25	4.75	0.25	0.027	0.119	15.85
Banana.....	...	100	...	100	21.00	1.10	0.60	0.007	0.042	5.56
Honey.....	30	30	24.36	0.12	0.001	0.005	2.44
Chicken.....	40	40	8.60	1.00	0.008	0.063	6.80
Corn.....	...	100	...	100	19.00	2.80	1.20	0.005	0.062	1.70
Sugar.....	20	10	10	40	40.00
Nut margarine	10	15	15	40	34.00
Coffee.....	200	200
Tea.....	...	200	200	400
Salt, 3 Gm.											
Total grams (calories 1,738).....					256.41	49.37	57.25	0.095	0.591	31.71	31.37

by Bauer and Aub⁴² in their studies of the calcium metabolism of a large number of normal persons. The results obtained in our patient could therefore be compared with those obtained by these authors in normal persons.⁴¹ Diet 2 (table 2) was obtained by the addition of 250 cc. of boiled skimmed milk a day to diet 1. Finally, a diet rich in native vitamins, calcium and phosphorus and somewhat higher in calories was utilized, diet 3 (table 3). The plan of the diet and medication during the entire time of intensive study is given in table 4.

The patient was given the control diet (diet 1) for forty-eight hours before the collection of specimens for analysis was begun. She was then given 0.6 Gm. of carmine alum lake in a gelatine capsule at 8 a. m. before breakfast. The collection of the feces for the period started with the first appearance of the carmine in the stools. After three days, the patient was given 0.6 Gm. of charcoal at 8 a. m. before breakfast. The appearance of charcoal in the feces thus marked the end of the carmine period and the beginning of the next three-day

42. Bauer, W., and Aub, J. C.: Studies in Inorganic Salt Metabolism: I. The Ward Routine and Methods, *J. Am. Dietet. A.* **3**:106, 1927.

About Nov. 1, 1927, slight edema of the face and ankles appeared with no other noteworthy changes. On November 11, he was taken ill with bronchopneumonia, and was removed to the hospital. The blood pressure was found to be elevated to 160, systolic; 110, diastolic, and the abnormal urinary condition was increased. Renal concentration tests disclosed a depression in function, while the phenolsulphonphthalein test and the blood nitrogen were normal. Hypercholesterolemia was present. Within a few weeks, the pneumonia cleared up, the nephritic condition changing little.

Following the patient's recovery from pneumonia, he developed cerebrospinal meningitis (epidemic type). On Dec. 2, 1927, during the course of meningitis, the abnormal urinary condition increased markedly while no retention of blood nitrogen or edema was noted. The recovery from meningitis was complete by Jan. 2, 1928. Aside from the anemia, the general condition improved rapidly. The blood cholesterol never dropped below 300 mg. per hundred cubic centimeters during any of the illnesses. The general condition of the patient steadily improved, and on February 1, the cells had practically gone from the urine and only moderate quantities of albumin were present. There was a gradual rise in blood pressure until by this time it measured 250, systolic; 130, diastolic. Aside from the increasing blood pressure, it appeared that the nephritis was becoming quiescent. The ophthalmoscopic examination, which had shown normal results prior to this time, disclosed a considerable choroidal exudate around the disks, but no hemorrhages were found. Progress seemed satisfactory except for the hypertension until February 25, when he developed a typical attack of convulsive uremia. This was controlled by intravenous injections of 10 per cent magnesium sulphate solution and hot packs. The urinary symptoms had increased, while the blood nitrogen and the phenolsulphonphthalein test remained normal. The eye-grounds on the day following the convulsions showed hemorrhages in the retina. During the following four months, rapid improvement was noted. The urinary condition was reduced considerably, and he was entirely free from symptoms except for headache which came and went at infrequent intervals. The albuminuric retinitis and anemia persisted.

In the summer of 1928, many changes for the worse developed. There was an increase in all pathologic urinary elements; the urinary concentration ability decreased, and there was a reduction in the phenolsulphonphthalein output. No great increase, however, was found in the blood nitrogen. A definite fall of the blood cholesterol appeared, and the blood pressure remained highly elevated. The patient slowly declined during the fall of 1928, and by December was confined to bed because of weakness, headache and gastro-intestinal disturbances. Coma with twitchings but with no convulsions followed. The blood nitrogen never rose to a high figure. Bronchopneumonia of the terminal type helped to shorten life. He died on Dec. 20, 1928, of uremic coma and bronchopneumonia.

Abstract of Autopsy Report.—The body was well developed and nourished; the skin and visible mucous membranes were pale with a tinge of yellow. Edema of the ankles and face was found, and the abdominal cavity was filled with a clear, serous fluid. Areas of bronchopneumonia were found in the left upper and lower lobes. The liver was enlarged and engorged with blood. The spleen was enlarged, measuring 15 by 17 by 4 cm. Bloody fluid was present in the stomach, and the mucous membrane showed many petechial hemorrhages.

Examination of the heart disclosed the following: It was enlarged, measuring 11 cm. at the base and the distance from apex to base was 12 cm. The valves were intact. The anterior mitral cusp contained on its aortic aspect a few yellowish patchy deposits. The aorta in its ascending portion and arch had rich

stool period. The fecal periods were differentiated throughout the study by the alternate administration of carmine and charcoal in this manner. The three-day stool specimens were dried, weighed, ashed and extracted as described by Bauer and Aub.⁴² The urine for the corresponding three-day periods was collected from 8 a. m. before breakfast on the first day, to 8 a. m. before breakfast on the fourth day; the patient always voiding in the morning before the beginning of the new period. A few cubic centimeters of chloroform and from 5 to 10 cc. of concentrated hydrochloric acid were added to the specimens of urine to preserve them and to keep the urine acid until the time of analysis, so that no ammonia would be lost. The total urinary output for each three-day period was well mixed, measured and examined by a routine urinalysis. An aliquot portion of the specimen was saved for chemical analysis.

The calcium contents of urine, feces, serum and spinal fluid were determined according to Fiske's method;⁴³ the phosphates of the urine, feces and serum by the method of Fiske and Subbarow,⁴⁴ and the urinary nitrogen by the method of Folin.⁴⁵ Blood hemoglobin was determined by the Newcomer method. The fecal nitrogen for each period was calculated as 10 per cent of the nitrogen intake for that period, and the total nitrogen output was estimated by adding the figures for the fecal and urinary nitrogen output.

The prolonged stay in bed and the low roughage in the diets caused the patient to become constipated, and either liquid petrolatum or cascara sagrada in tablet form was used as a cathartic. The calcium content of this medication, as given by Bauer and Aub,⁴² as well as the calcium and phosphorus content of the cod liver oil concentrate, as determined by us, was added to the daily intake whenever these substances were given. Furthermore, the calcium content of the calcium lactate used in the diet was determined by analysis.

METABOLIC OBSERVATIONS

The results of period 1 (table 5), during which the patient received the low calcium, low vitamin, neutral diet (diet 1, table 1), demonstrate strikingly the tendency of the patient to lose calcium and phosphorus. An average normal subject under a similar regimen has a negative calcium balance of 0.46 Gm. of calcium, or 6.7 mg. per kilogram, and is in approximate phosphorus equilibrium.⁴⁶ In periods 1 and 2, the patient showed an average loss of 1.79 Gm. of calcium, 45 mg. per kilogram, and 0.64 Gm. of phosphorus in three days. This is all the more significant since the patient received sufficient calories, as shown by the gain in body weight and the positive nitrogen balance. In periods 3 and 4, the calcium intake was quadrupled and the phosphorus intake greatly increased by adding 250 cc. of boiled skimmed

43. Fiske, C. H.: To be published.

44. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375, 1925.

45. Folin, O.: Kjeldahl's Method for the Determination of Nitrogen, *Laboratory Manual of Biological Chemistry*, New York, D. Appleton & Company, 1925, p. 59.

46. Bauer, W.: Personal communication to the authors.

deposits of this yellowish, fatty material and presented a picture of atherosclerosis. Fatty degeneration was found in the heart muscle.

The right kidney weighed 182 Gm.; the left, 197 Gm. Embryonal lobulations were found in both. When the capsule was stripped, the surface of the kidney was seen to be richly speckled with distinct, small, yellowish crystals which were found to be fat. On the cut surface, the markings were found to be distinct. The cortex and columns of Bertini were extensively speckled with flakelike yellowish fatty deposits. The renal arteries and the arteries seen on the cut surfaces of the kidneys were found to have undergone profound arteriosclerotic changes.

Microscopic Examination.—All sections were stained and studied with hematoxylin-eosin, van Gieson's, Weigert's elastic tissue stain, sudan III and Giemsa's stain. Polariscopic examinations were done when fat was found.

The aorta (section of a yellow patch) showed extensive hyperplasia of the elastic tissue of the intima. Fatty degeneration of the intima was pronounced, and there was extension of fat into the media. The fatty substance showed evidence of confluence and formed spaces in the intima filled with cellular debris. Some of the fat was doubly refracting and was considered to be cholesterol ester. In the intima, the connective tissue was considerably increased. The processes in the intima had the appearance of atheromatous cavities before the stage of ulcer formation. In the aortic wall, the arterioles had thickened walls. This thickening was due to hypertrophy of the muscular tissue of the media.

A picture of chronic passive congestion was found in the spleen. The vessels appeared to be normal. No fat was found.

There were no demonstrable changes in the intimal layers of any of the vessels of the skeletal muscle. The medial coat of the arterioles and smaller arteries showed practically no change.

With sudan III, considerable fat was seen in the periphery of the lobules of the liver. Much of it doubly refracted polarized light. The walls of the liver arterioles in places were slightly thickened by virtue of fatty degeneration of the intima. The media was not increased.

There was a decided increase in the interstitial fibrous tissue of the kidneys. Many glomeruli were completely fibrosed; others were enlarged and showed an increase in cellularity. Occasionally, a glomerulus was seen in which some loops were fibrosed and adjacent loops were thrombosed. Characteristic crescent formations were numerous. Almost universally, Bowman's capsules were thickened with fibrous tissue. No evidences of acute inflammatory processes were present. The epithelium of the convoluted tubules was everywhere diseased. Fatty and granular degeneration with swelling and various stages of disintegration of the epithelial cells was the chief change. In places no lining epithelial cells were found, the basement membrane being covered only by cell debris. With fat stains the epithelium of the convoluted tubules was found to be loaded with fat. A great deal of fat was also present in the interstitial tissue. Practically all of this fat doubly refracted polarized light and was considered, therefore, to be cholesterol ester.

The arteries and arterioles of the kidney were universally damaged. The renal, arcuate and interlobular arteries for the most part had undergone definite arteriosclerotic changes. The media was reduced in size, and fatty degeneration characterized the swollen intimal tissues the elastic tissue of which had become hyperplastic. In some of the interlobular arteries, the media was thickened, and the intima increased due to connective tissue proliferation, no fatty changes being seen in them. At the boundary zone between the swollen intima and thickened media,

TABLE 5.—Calcium, Phosphorus and Nitrogen Metabolism per Three-Day Period

Period	Kg.	Intake			Output			Total			Metabolic Balances			Metabolic Balances per Kilogram			Comment	
		Weight of Patient	Cal- cium, Gm.	Phos- phorus, Gm.	Nitro- gen, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.	Nitro- gen, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.	Nitro- gen, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.	Nitro- gen, Gm.				
1	39.2	0.33	1.83	23.70	0.80	1.32	19.32	1.45	1.21	2.37	2.25	2.53	21.69	-1.92	-0.70	+ 2.01	+0.051	Control diet 1, low in calcium, phosphorus and vitamins
2	40.4	0.32	1.83	23.70	0.88	1.57	20.81	1.10	0.83	2.37	1.98	2.40	23.18	-1.66	-0.57	+ 0.52	+0.013	
3	40.8	1.24	2.55	27.78	1.14	2.14	29.30	0.77	0.45	2.78	1.91	2.59	32.08	-0.64	-0.04	- 4.30	-0.105	
4	40.7	1.24	2.55	27.78	0.99	1.66	22.59	1.12	0.66	2.78	2.11	2.32	25.35	-0.87	+0.23	+ 2.43	+0.060	Diet 1 as in periods 1 and 2, plus 250 cc. boiled skimmed milk daily
5	41.4	1.24	2.55	27.78	1.02	2.10	22.44	1.07	0.57	2.78	2.09	2.67	25.22	-0.85	-0.12	+ 2.56	+0.062	
6	41.6	1.25	2.55	27.78	0.94	2.12	21.61	0.20	0.19	2.78	1.14	2.21	24.39	+0.11	+0.31	+ 3.39	+0.081	
7	41.6	2.00	2.55	27.78	0.90	1.65	20.46	0.74	0.58	2.78	1.64	2.23	23.24	+0.36	+0.52	+ 4.54	+0.109	Same diet and medication as in periods 5 and 6, plus 18 osceol tablets daily
8	41.8	2.00	2.55	27.78	0.74	1.46	24.41	0.63	0.54	2.78	1.37	2.00	27.29	+0.63	+0.55	+ 0.49	+0.012	
9	42.5	2.00	2.55	27.78	0.63	1.21	21.42	0.31	0.32	2.78	0.94	1.53	24.20	+1.06	+1.02	+ 3.58	+0.084	
10	42.1	2.00	2.55	27.78	0.75	1.38	21.03	0.14	0.12	2.78	0.89	1.50	23.81	+1.11	+1.05	+ 3.97	+0.094	Same diet and medication as in periods 7 and 8, plus daily treatment with ultraviolet light
11	42.0	2.00	2.55	27.78	0.71	1.35	21.47	0.21	0.26	2.78	0.92	1.61	24.25	+1.08	+0.94	+ 3.53	+0.092	
12	42.0	2.00	2.55	27.78	0.46	1.23	19.68	0.08	0.08	2.78	0.54	1.31	22.46	+1.46	+1.24	+ 5.32	+0.127	
13	42.8	2.02	2.55	27.78	0.45	1.23	21.45	0.30	0.43	2.78	0.75	1.66	24.23	+1.25	+0.89	+ 3.55	+0.083	Control diet 1, same as in periods 1 and 2
14	42.5	0.35	1.83	23.70	0.39	1.39	18.51	0.13	0.19	2.37	0.52	1.58	20.88	-0.17	+0.25	+ 2.82	+0.066	
15	42.8	0.35	1.83	23.70	0.42	1.25	18.19	0.13	0.41	2.37	0.55	1.65	20.56	-0.20	+0.18	+ 3.14	+0.073	
16	43.0	5.74	2.55	27.78	0.64	0.62	12.88	1.24	0.36	2.78	1.88	0.98	15.66	+3.86	+1.57	+12.12	+0.282	Same diet and medication as in periods 9 to 13, plus calcium lactate
17	43.4	5.74	2.55	27.78	0.63	0.29	13.40	2.62	0.62	2.78	3.25	0.91	16.18	+2.49	+1.64	+11.60	+0.267	
18	43.4	5.75	2.55	27.78	0.49	0.39	15.61	0.93	0.26	2.78	1.42	0.65	18.39	+4.33	+1.90	+ 9.49	+0.219	
19	43.7	0.35	1.83	23.70	0.34	1.11	16.33	0.63	0.35	2.37	0.97	1.46	18.70	-0.62	+0.37	+ 5.00	+0.114	Control diet 1, same as in periods 1 and 2
20	43.2	0.36	1.83	23.70	0.22	1.05	17.55	0.12	0.36	2.37	0.34	1.41	19.92	+0.02	+0.42	+ 3.78	+0.087	
21	43.3	2.03	9.00	27.78	0.07	4.97	22.50	0.25	0.34	2.78	0.32	5.31	25.28	+1.67	+3.79	+ 2.50	+0.058	
22	43.4	2.02	9.00	27.78	0.08	6.10	23.92	0.18	0.24	2.78	0.26	6.34	26.70	+1.76	+2.63	+ 1.08	+0.025	Same diet and medication as in periods 9 to 13, plus disodium acid phosphate
23	43.5	2.03	9.00	27.78	0.09	6.94	20.69	0.29	0.31	2.78	0.38	7.25	23.47	+1.65	+1.75	+ 4.31	+0.039	
24	43.8	2.03	9.00	27.78	0.13	5.92	19.42	0.21	0.28	2.78	0.34	6.20	22.20	+1.60	+2.80	+ 5.58	+0.127	
25	43.5	0.36	1.83	23.70	0.28	1.88	17.07	0.24	0.38	2.37	0.52	2.26	19.44	-0.16	-0.43	+ 4.26	+0.098	Control diet 1, same as in periods 1 and 2
26	43.4	0.35	1.83	23.70	0.38	1.29	15.31	0.10	0.39	2.37	0.48	1.68	17.68	-0.13	+0.15	+ 6.02	+0.139	
27	44.4	5.75	9.00	27.78	0.23	4.33	18.28	1.24	0.75	2.78	1.47	5.08	21.06	+4.28	+3.92	+ 6.72	+0.151	
28	44.1	5.75	9.00	27.78	0.17	5.00	16.90	1.09	0.44	2.78	1.26	5.44	19.68	+4.49	+3.56	+ 8.10	+0.181	Same diet and medication as in periods 9 to 13, plus calcium lactate and disodium acid phosphate
29	44.9	5.75	9.00	27.78	0.22	5.19	18.62	0.76	0.33	2.78	0.98	5.52	21.40	+4.77	+3.48	+ 6.38	+0.142	
30*	45.5	5.78	9.00	34.95	0.22	5.26	21.12	1.71	0.86	3.50	1.93	6.11	24.62	+3.85	+2.89	+10.33	+0.227	
31*	45.5	5.78	9.00	34.95	0.22	5.26	21.12	1.71	0.86	3.50	1.93	6.11	24.62	+3.85	+2.89	+10.33	+0.227	Diet 3 plus cod liver oil, osceol and ultraviolet light as above, also calcium lactate and disodium acid phosphate
32*	45.5	6.08	9.41	34.95	0.50	5.59	21.65	0.50	0.25	3.50	1.90	5.84	25.15	+3.08	+3.57	+ 9.80	+0.215	
33*	46.5	6.08	9.41	34.95	0.50	5.59	21.65	0.50	0.25	3.50	1.00	5.84	25.15	+5.08	+3.57	+ 9.80	+0.211	

* The results of periods 30 and 31 were obtained by dividing one six-day period by 2 for the purpose of comparison. The results of periods 32 and 33 were obtained similarly.

vacuoles were found in some areas, and empty spaces were seen also, scattered throughout the media.

The renal arteriolar walls were thickened everywhere, and the vascular lumina was almost obliterated in some places. Two definite types of changes were found occasionally in the same microscopic field. In some arterioles the media was hypertrophied, and the intima was either intact or was thickened from a proliferation of connective tissue; in others, the media was reduced and the intima was thickened with fatty degeneration or with increase of the connective tissue. No necrotic changes were found in the walls.

COMMENT

The Clinical Syndromes.—The changeableness of the symptoms of chronic nephritis often leads to confusion in the proper interpretation of the clinical picture at some stages of the disease. This variability of the symptoms is well represented in the illustrative case reported here. The symptoms were seen to occur at times in such combinations as to suggest the diagnosis of lipoid nephrosis; at other times, the symptom arrangement would lead one to suspect malignant hypertension. For the purpose of clarity, it is well to classify the leading symptoms into five syndromes as follows: (a) urinary; (b) nitrogen retention; (c) hypertension; (d) edema and (e) uremic.

All of the syndromes except the nitrogen retention were seen to appear at one time or other during the course of the disease. In some periods of the disease, all the syndromes except the nitrogen retention were present at one time; and then one by one they disappeared, either to recur later or never to return at all. On June 7, 1927, the urinary manifestations, the edema, and hypercholesterolemia with no hypertension, hematuria or nitrogen retention, produced the clinical features resembling lipoid nephrosis; while in March, 1928, the marked hypertension and a severe retinitis without nitrogen retention and edema constituted a clinical picture resembling malignant hypertension, as shown in the accompanying table.

During the entire course of the disease, the nitrogen retention syndrome was absent. When uremia developed on Feb. 2, 1928, there was no retention of nitrogen, although the uremia was convulsive in nature. At the end of the course, in December, 1928, twitching developed, but no convulsions followed; the patient had the clinical picture of true uremia, yet only slight nitrogen retention was present.

The renal function tests were of interest in that the phenolphthalein was excreted in a normal fashion throughout the course of the disease until toward the end. The earliest sign of impairment of renal function was elicited by the concentration and dilution test of Vollhard. No impairment was noted until January, 1928, in the fifth year of observation. It appears probable, therefore, that nephritis must be fairly well advanced, in some cases at least, before the ordinary renal function tests

It was evident that the administration of phosphorus alone increased the retention of calcium just as the addition of calcium alone increased the retention of phosphorus.

These results clearly indicated the advisability of giving large amounts of both calcium and phosphorus, as well as large amounts of vitamins A and D, and this was, accordingly, done in periods 27, 28 and 29. As can be seen in table 5 and columns K in figure 1, the response of the patient was most gratifying.

In periods 30, 31, 32 and 33, part of the calcium and phosphorus which had previously been given as salts was given by means of foods (diet 3, table 3) rich in calcium and phosphorus. The fact that there was no significant change in the retention of the bone-forming elements indicates that administration of calcium and phosphorus in the form of salts is as efficacious as giving them in the form of native food content.

Phosphorus Metabolism.—In table 6, data are presented in a form that makes possible the comparison of the "theoretical" phosphorus balance with the actually determined phosphorus balance. The purpose of such a comparison is to discover to what degree retention and excretion of calcium and phosphorus denote alteration in the metabolism of bone. The term "theoretical phosphorus balance" refers to the phosphorus balance calculated from the nitrogen and calcium balances. The theoretical phosphorus retained or lost with nitrogen can be calculated with considerable confidence whereas the theoretical phosphorus retained or lost with calcium rests on the assumption that all the phosphorus not metabolized with nitrogen takes part in bone metabolism as calcium phosphate. It is consequently apparent that the extent to which the "theoretical phosphorus balance" and the actually determined phosphorus balance coincide provides a means of learning to what degree the phosphorus retained or excreted reflects changes in the metabolism of bone. The theoretical phosphorus retained or lost as protein has been calculated from the ratio of $\frac{\text{nitrogen}}{\text{phosphorus}} = \frac{17.4}{1}$ and the phosphorus retained or lost as bone from the ratio $\frac{\text{calcium}}{\text{phosphorus}} = \frac{2.3^{50}}{1}$. The method

50. Example:

Period 1. Calcium balance determined = 1.92 Gm.

$$\begin{array}{lcl} \text{Theoretical phosphorus balance calculated} & 1.92 & 2.3 \\ \text{from calcium} & = \frac{\quad}{x} :: \frac{\quad}{1} & = -0.86 \text{ Gm.} \end{array}$$

$$\text{Nitrogen balance determined} = 2.01 \text{ Gm.}$$

$$\begin{array}{lcl} \text{Theoretical phosphorus balance} & \frac{2.01}{x} :: \frac{17.4}{1} & = +0.12 \text{ Gm.} \end{array}$$

$$\text{Total theoretical phosphorus balance} = -0.86 + 0.12 = -0.74 \text{ Gm.}$$

are of much value in the study of the condition. It emphasizes the inadequacy of the usual renal function tests in detecting early impairment. Of all the syndromes, the urinary was the most constant. The urine was never normal from the onset to the end. It seems fair to suppose that of all the tests and measurements, the close study of the urine, for practical purposes, is the most instructive and important.

The Hypercholesterolemia and the Lipoid Deposits in the Various Organs.—The hypercholesterolemia in this case appeared to antedate the doubly refracting lipid deposits in the kidney and aorta. This is assumed to be the case because the lipoids were not found in the urine until at least two years after a definite hypercholesterolemia had become established. It was found in animal experimentation (unpublished at present) that lipid deposits in the renal tubular epithelium are followed shortly (in from ten to fifteen days) by lipoids in the urine. Judging from the data presented, it would seem that a defective fat metabolism was a primary factor and the lipid deposits in the kidney and blood vessels were results of a combination of forces, one of them being a hypercholesterolemia. It has become fairly well established in the minds of many that lipid nephrosis is primarily a disturbance in cholesterol and protein metabolism followed by morphologic changes in the kidney epithelium with subsequent deposits of lipoids in the renal tissue. This theory is subscribed to by many observers, including Munk,¹ Lowenthal,² Epstein,³ Fahr,⁴ Kollert and Finger⁵ and others. The nature of the factors producing hypercholesterolemia is not known. It is undecided at present whether or not the factors that cause pure lipid nephrosis are the same as those responsible for the nephrotic features of some cases of glomerulonephritis. Elwyn⁶ emphasized the importance of glomerular damage in the production of lipid nephrosis. He believed that the injury to the glomerulus was the primary factor in the disturbance. Stepp⁷ also considered the damage of the renal epithelium to be the chief cause of the hypercholesterolemia. From time to time

1. Munk, F.: *Pathologie und klinik der nierenkrankungen*, Vienna, Urban and Schwarzenberg, 1925.

2. Lowenthal, K.: *Zur Frage der Lipoid Nephrose*, Virchows Arch. f. path. Anat. **261**:109, 1926.

3. Epstein, A. A.: *Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation*, Am. J. M. Sc. **154**:638, 1917.

4. Fahr, T.: *Beitrage Zur Frage der Nephrose*, Virchows Arch. f. path. Anat. **239**:32, 1922.

5. Kollert, V., and Finger, A.: *Ueber die Beziehungen der Nephritis zum Cholesterin (Lipoid) Stoffwechsel*, München. med. Wchnschr. **65**:816, 1918.

6. Elwyn, Herman: *The Pathogenesis of Lipoid Nephrosis*, Arch. Int. Med. **38**:346 (Sept.) 1926.

7. Stepp, W.: *Ueber den Cholesteringehalt des Blutes bei verschiedenen Formen der Bright'schen Krankheit*, Deutsches Arch. f. klin. Med. **127**:439, 1918.

amount of phosphorus available in the diet was not entirely utilized in conjunction with calcium. The actual total phosphorus output in these periods (average 0.28 Gm. per diem) is the lowest that occurred during the study of this case and is as low as any we have been able to find recorded in the literature. It may well be the result of the endogenous metabolism of protein and of bone, and as such it would not be available in forming new bone. According to this concept, all the available phosphorus was used to form calcium phosphate and the additional calcium retained was possibly deposited as calcium carbonate in excess of the normal ratio.

In periods 21 to 24 (table 6) inclusive, the converse of this situation was established, for, instead of increasing the calcium separately, the phosphorus was increased without a corresponding addition of calcium. On a phosphorus intake of 9 Gm. for a three-day period, an average of 1.8 Gm. of phosphorus was retained in excess of that theoretically expected. To be sure, the increased amounts used lead to an increase in the absolute error of measurement but not to a degree sufficient to account for the results. It might be expected that, with the deposition of this large amount of phosphorus, all available calcium would have been utilized. The explanation, again, may lie in the fact that the calcium excreted was not available inasmuch as it represented the endogenous calcium metabolism of bone. This explanation is supported by the low total calcium output (average 0.11 Gm. per diem) in these periods, the output being lower than in any other periods in our study or in any others reported in the literature. The form in which the phosphorus was utilized cannot be stated, although it is conceivable that phosphate salts of other cations such as magnesium may have been deposited.

Observations on the Blood and Spinal Fluid.—All observations on the blood and spinal fluid were made on specimens drawn after a fast of from fourteen to sixteen hours' duration. The calcium and inorganic phosphorus contents of the serum and the concentration of the peripheral hemoglobin and red blood cells, which were determined at frequent intervals during ten months of observation, are given in table 7. The calcium content of the serum was 10.7 mg. per hundred cubic centimeters on June 5, 1928, during period 1, and remained always within the accepted limits of normal for the entire time of observation. The inorganic phosphorus content was 2.24 mg. per hundred cubic centimeters on June 5, 1928, before treatment was started, and remained definitely below normal throughout the course of treatment. The two highest figures, 2.64 and 2.94 mg. per hundred cubic centimeters, were obtained on Aug. 10, 1928, and on Nov. 27, 1928, respectively, during periods of high phosphate medication. There was

it has been advocated that the main factor in nephritis is not the kidney damage but some extrarenal disturbances which result in kidney damage. Graves,⁸ in 1831, was unwilling to accept Bright's interpretation of albuminous urine as indicative of primary renal disease. He regarded the albuminuria as a cause and the pathologic changes in the kidney as the result of it. Graves considered nephritis as a general disturbance and believed that the liver or some other organs were primarily responsible for the condition. A similar theory has been expressed and experimental data submitted to substantiate it by Andrews, Thomas and Welker.⁹ They contended that there are changes in the osmotic equilibrium associated with alterations in the mineral salt balance which induce increased tissue permeability. This allows passage of tissue proteins into the blood which are foreign to the circulation, and they are excreted. They suggest that nephritis is comparable to diabetes in the sense that protein metabolism is interfered with by some means, so that oxidation is incomplete and the processes stop at a stage where the products of nitrogenous metabolism are toxic and are eliminated. That hypercholesterolemia in itself is not sufficient for the production of lipid deposits in the kidney and other tissues was proved by Chalatow.¹⁰ He showed that when the cells are injured a slight rise in blood cholesterol is sufficient to cause deposits of lipid in the injured cells.

The relationship of the lipid changes in the kidney to the edema of nephritis has been reported elsewhere¹¹ and therefore will not be discussed here. In the autopsy report, it is seen that a well developed arteriosclerosis was found in the ascending portion of the aorta and an arteriosclerotic plaque was present on one of the mitral cusps. The murmur that was first heard about April 1, 1927, was undoubtedly produced by the lesion on the mitral valve. In the presence of a long standing hypercholesterolemia, it is not unusual to find these lipid deposits in the valve. In another case, one of pure lipid nephrosis, reported by Murphy and Warfield,¹² a similar picture of arteriosclerosis was found in the aorta, and the aortic leaflet of the mitral valve showed a similar lesion as described here. 'The development of a profound

8. Graves, R., quoted by Bartels, in Ziemssen's *Cyclopedia of Practice of Medicine*, 1877, p. 15.

9. Andrews, Edmund; Thomas, William A., and Welker, William F.: *Albuminuria in the Mechanism of Detoxification*, *Arch. Int. Med.* **43**:139 (Jan.) 1929.

10. Chalatow, S. S.: *Die Anisotrope verfettung in Lichte der Pathologie des Stoffwechsels*, Jena, Gustav Fischer, 1922.

11. Murphy, Francis D.: *Chronic Nephritis With and Without Edema: A Study of Cholesterol in These Conditions*, *J. Clin. Investigation* **5**:63, 1927.

12. Murphy, Francis D., and Warfield, Louis M.: *Lipoid Nephrosis*, *Arch. Int. Med.* **38**:449 (Oct.) 1926.

after treatment may have been due to the arrest of the process. The Wassermann and Kahn tests of the blood were negative on repeated examination during the year of observation.

Lumbar puncture was not done until March 1, 1929, ten months after treatment had started, because of the tenderness and deformity of the spine before this time. The fluid was clear, and the pressure normal. The Wassermann reaction and the colloidal gold curve were negative. The calcium content was 6.3 mg. per hundred cubic centimeters, and the calcium content of blood serum taken simultaneously was 11.1 mg. per hundred cubic centimeters.

The inorganic phosphorus content of the spinal fluid was 0.84 mg. and of the serum 2.20 mg. per hundred cubic centimeters. According to Fremont-Smith,⁵³ the calcium content of the spinal fluid is normal, but the phosphorus concentration is strikingly low. The normal proportionality of $\frac{\text{spinal fluid calcium}}{\text{serum calcium}}$ and of $\frac{\text{spinal fluid phosphorus}}{\text{serum phosphorus}}$ was present in this patient in spite of the extremely low phosphorus values.

ROENTGEN OBSERVATIONS

Figures 2, 3 and 4 show the appearance of the skull, pelvis and hands compared with a normal hand. The extreme degree of decalcification is evident. Figures 5, 6 and 7 show the appearance of the same parts of the body on Sept. 12, 1928, approximately three months after the institution of treatment. The roentgen report at that time was: "The thinning and atrophy of the bones is definitely less marked than when the patient was last seen. The bones are, however, somewhat less dense than normal even at this time."

By the time the last metabolic observations were concluded, three months from the beginning of the studies, the patient felt much stronger, the exquisite tenderness of the ribs and other bones had disappeared, and anemia was less marked. The patient then weighed 103 pounds (46.7 Kg.) in contrast with 86½ pounds (39.2 Kg.) before treatment. Proper orthopedic measures were instituted owing to the cooperation of Dr. Joseph H. Shortell of the Boston City Hospital and later of Dr. Mark Rogers of the Beth Israel Hospital. The effects of the dietary and orthopedic treatment were so striking that the patient was able to be up and about and left the hospital two weeks after the final metabolic studies had been completed. The beneficial dietary and orthopedic procedures were continued at home. During the past year, the patient has felt entirely well and has done all the housework for her family of four. She comes to the hospital twice weekly for ultraviolet irradiation. The skeletal measurements of the patient before, during

53. Fremont-Smith, F.: Personal communication to the authors.

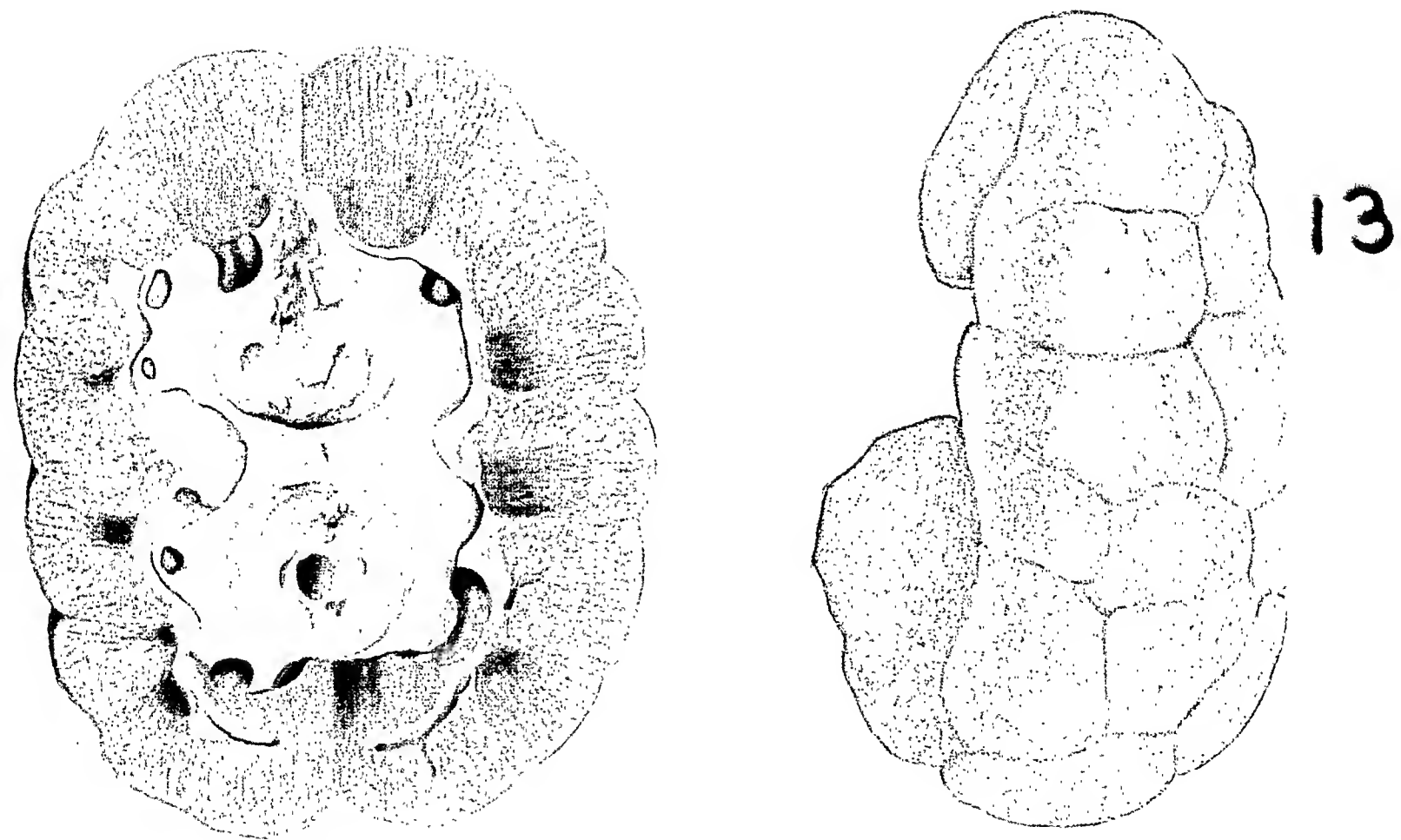


Fig. 1.—At left, right kidney, showing the flaky yellowish deposits of lipoids distributed uniformly throughout the organ; at right, the surface of the same specimen. Water color painting.

Dixon,¹¹ and Wilder¹² reported cases showing undoubted evidences of hyperparathyroidism with osteitis fibrosa cystica. Their cases resemble that of our patient in that softening of the bone with decalcification was present and in that the condition was benefited by a diet high in vitamin D and daily treatment with ultraviolet light. In contrast with our patient, however, their patients showed an elevated level of the serum calcium, multiple benign giant cell tumors of the bones, tumors of the parathyroid glands and bone cysts. These facts, together with the remarkable manner in which our patient recovered her strength and maintained it on a diet high in vitamins A and D and ultraviolet light treatment and without surgical excision of the parathyroid glands, indicate that the condition in our patient was not due to a primary disorder of the parathyroid glands, and differs fundamentally from the cases of osteitis fibrosa cystica reported.

Why our patient required more vitamin substances than other, normal persons is obscure. Certain features strongly suggest, however, that osteomalacia, as observed by us, is a form of adult rickets.

Clinical Similarities Between Osteomalacia and Rickets.—Clinically, the same bones as in rickets were most prominently affected. The roentgen appearance of the epiphyses was likewise strikingly similar to that observed in adult rickets by Hutchison and Stapleton.³³ The softening of the bones appeared at the time of year in which the highest percentage of the manifestations of rickets occurs.⁵⁵

Metabolic Similarities.—It is now established that there are four factors, any one of which plays an important part in the production of rickets: calcium, phosphorus, vitamin D and ultraviolet radiation.⁵⁶ Orr, Holt, Wilkins and Boone⁵⁶ stated that cod liver oil and ultraviolet light irradiation facilitate absorption of calcium and phosphorus from the intestine in rickets. In this connection, it is of interest that the fecal calcium and phosphorus output in our patient became conspicuously less after the administration of cod liver oil concentrate and ultraviolet light. Whether this was due to increased absorption or to decreased excretion of calcium into the bowel, or to both, cannot be stated. In any event, these observations are in accord with those in rickets. Cod liver oil contains vitamins A and D. Irradiation with ultraviolet light may ameliorate conditions due to vitamin D deficiency, but cannot act as a substitute for this factor when it is completely absent from the diet. When given with vitamin D, however, it greatly increases

55. Lawrens, H.: Physiologic Effects of Radiation, *Physiol. Rev.* 8:1, 1928.

56. Orr, W. J.; Holt, L. E.; Wilkins, L., and Boone, F. H.: The Calcium and Phosphorus Metabolism in Rickets, with Special Reference to Ultraviolet Ray Therapy, *Am. J. Dis. Child.* 26:362 (Oct.) 1923.



MATERIAL

Since 1922, twenty-six cases of lymphosarcoma were admitted to the Montefiore Hospital. Of these, seven presented neurologic signs, four of which were verified post mortem. Three of the cases presented signs of compression of the spinal cord, the remaining one showing involvement of the brain (table).

Cases of Lymphosarcoma with Involvement of the Nervous System

No.	Sex*	Age	Duration of Illness	Onset		Clinical Diagnosis	Neurologic Diagnosis	Response to Deep Roentgen or Radium Treatment	Observations from Autopsy or Biopsy
				General Symptoms	Neurologic Signs				
1	♀	61	1 year 9 months	Gradual	Gradual	Lymphosarcoma	Extramedullary neoplasm	Improvement early without any response later (deep roentgen only)	Generalized lymphosarcomatosis with metastasis to dura
2	♂	40	1½ years	Sudden	Sudden	Lymphosarcoma; hydrothorax	Herpes zoster	Relief early; no response later (deep roentgen only)	Generalized lymphosarcoma; pleural effusion; extramedullary neoplasm
3	♂	32	9 months	Sudden	Sudden	Neoplasm of right lung	Metastasis to cord; possibility of subacute combined degeneration	Early improvement; no response later	Lymphosarcoma of right lung; empyema; extramedullary deposits
4	♂	45	1 year 11 months	Sudden	Sudden	Generalized lymphosarcoma	Generalized lymphosarcoma with involvement of the meninges at the base of the skull	Temporary remission of glandular enlargement early; pain in this case was not relieved	Generalized lymphosarcomatosis with invasion of middle and posterior fossae
5	♂	64	Discharged in 1922 and not heard from since	Sudden	Sudden	Lymphosarcoma	Lymphosarcoma with invasion of posterior cranial fossa	Early improvement with recession of enlargements and symptoms	Biopsy; lymphosarcoma
6	♂	37	7 months	Sudden	Gradual	Lymphosarcoma of left lung with metastasis	Lymphosarcoma with metastasis to vertebral column	Improvement early with no response later (roentgen and radium)	Pleural exudate containing tumor cells
7	♀	38	8 months	Sudden	Gradual	Lymphosarcoma of neck	Left peripheral facial palsy	No benefit from either roentgen or radium (roentgen and radium)	Biopsy; lymphosarcoma

* In this column, ♂ indicates male; ♀ female.

REPORT OF CASES

Group 1: Cases Showing Involvement of the Central Nervous System Which Came to Autopsy (table).—CASE 1.—M. H., a woman, aged 61, entered the Montefiore Hospital on Feb. 21, 1924. Early in January, 1923, she had complained of a heavy feeling in the abdomen and a dull aching pain in the lower left side of the chest, later followed by attacks of sharp pains in the hypogas-

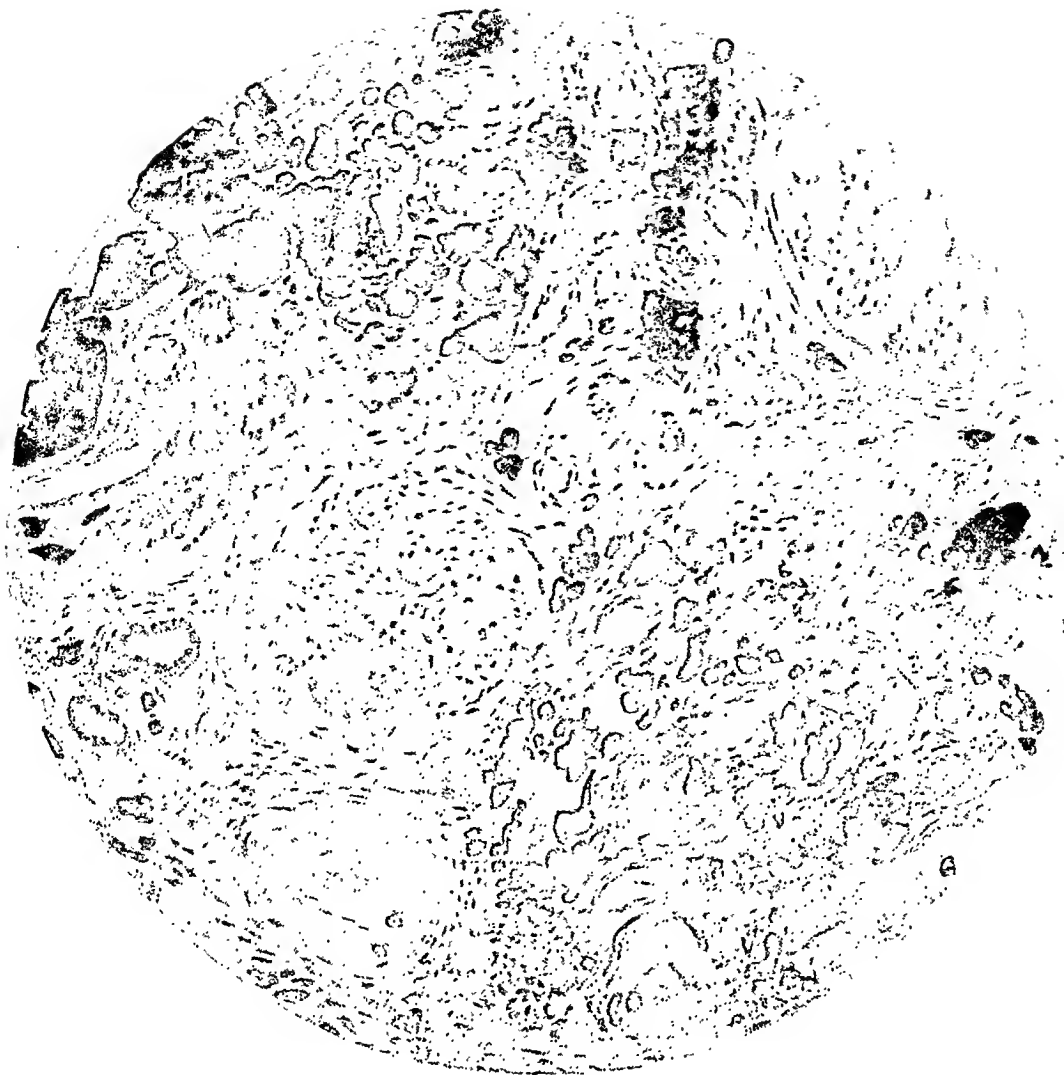


Fig. 2.—The extensive deposits of lipoid substances in the tubular epithelium and in the interstitial tissue. Hand colored photomicrograph.

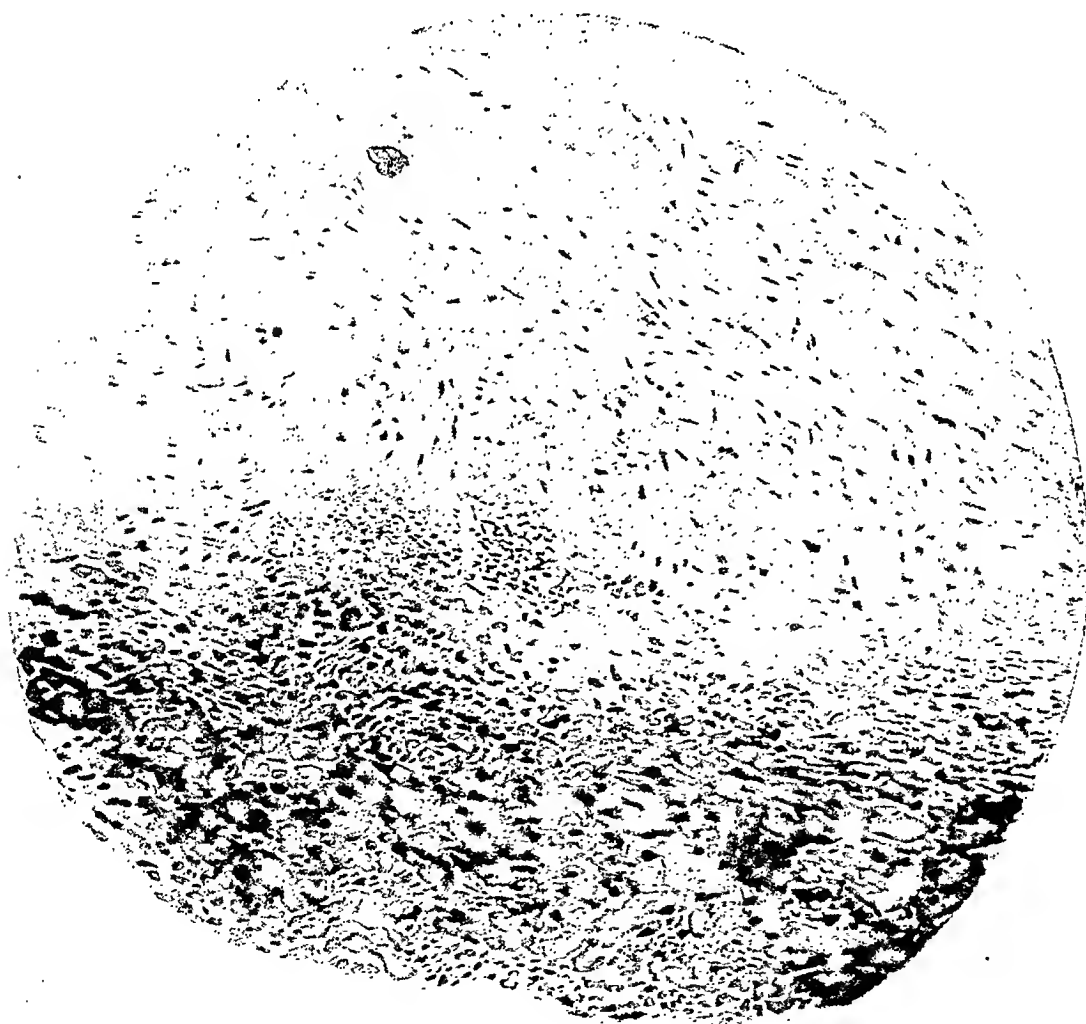


Fig. 3.—Section through a yellowish plaque in the aorta demonstrating the deposits of lipoid substances in the intima. Hand colored photomicrograph.

a continuous sheet of tumor tissue was found along the right lateral surface of the spinal canal adherent to the vertebrae and the dura. The tumor tissue apparently had grown into the canal through the intervertebral foramina.

Sections of the spinal cord of the midthoracic region showed (fig. 2) the tumor mass situated extradurally. The vessels of the cord were slightly thickened and congested. On one side the nerve roots were infiltrated by the tumor cells. In places the dura was replaced by the tumor, which grew in two directions. The spinal cord, with the exception of the roots, did not show any marked signs



Fig. 2.—Midthoracic section of cord showing lymphoid mass situated extradurally. Van Gieson stain; $\times 30$.

of compression. The microscopic appearance of the tumor tissue conformed to the microscopic observations of the tumor found elsewhere in the body.

The symptoms in this case began one and one-half years before admission to the hospital with rapid progression. With the exception of the herpes zoster caused by the invasion of the nerve roots, the neurologic signs were rather scanty in spite of a definite extramedullary

Numerous extramedullary lymphoid masses were deposited in the posterior portion at various levels of the spinal cord, chiefly in the upper thoracic region.

Microscopic Observations: Sections of the spinal cord at this level showed a degeneration (fig. 3) of the posterior column and posterior roots. Under the low power lens the process resembled the involvement seen in tabes dorsalis. With special stains and higher magnification the changes of the posterior columns were seen to be the same as those found in compression of the cord. With victoria blue stain, isomorphous gliosis was found instead of condensation of the glial elements as seen in tabes dorsalis.

Microscopic Diagnosis.—The diagnosis was: compression of the cord causing degeneration of the posterior columns.

The duration of illness in this case was nine months, with predominance of the neurologic signs. The absent deep reflexes and the definite signs of the posterior column suggested a diagnosis of tabes dorsalis. The definite sensory level precluded such a diagnosis. The

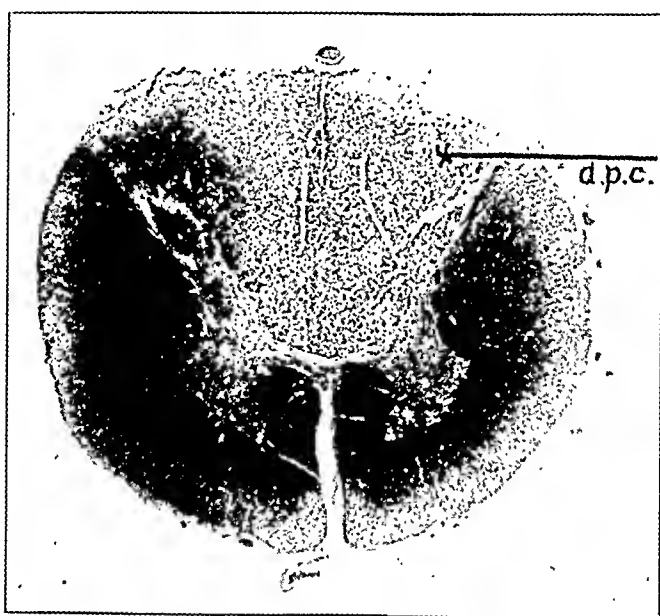


Fig. 3.—Section of thoracic region of cord showing degeneration of the posterior columns (*d.p.c.*). Weil stain; $\times 30$.

gross microscopic picture was that of tabes; examination with higher magnifications showed the condition to be a degeneration due to compression, with the absence of condensation of glial fibers as seen in tabes and multiple sclerosis as shown by Weil and one of us⁷ (Davison).

CASE 4.—J. H., a man, aged 45, a bookkeeper, was admitted to the Montefiore Hospital on Feb. 11, 1929. In April, 1927, he had noticed an enlargement of the glands of the right groin, which on deep roentgen treatment disappeared within from two to three weeks. In October, 1928, a large gland appeared in the left side of the neck, followed by diplopia, paresis of the left abducens muscle and bilateral optic neuritis. Shortly after a left supranuclear facial and oculomotor

7. Weil, A., and Davison, C.: Changes in the Spinal Cord in Anemia, Arch. Neurol. & Psychiat. 22:966 (Nov.) 1929.

arteriosclerosis in these young patients who have diseases characterized by hypercholesterolemia leads one to suspect that a high fat diet, especially one rich in cholesterol fat, may be more injurious than is commonly supposed. Joslin¹³ questioned the advisability of giving a diabetic patient a diet rich in cholesterol, especially if the patient has a hypercholesterolemia or signs of arteriosclerosis.

These clinical observations on the relationship of hypercholesterolemia are in accordance with the experimental work done on this subject. Ignatowski¹⁴ produced an infiltration of fat in the intima by feeding rabbits with egg yolk. In 1910, Stuckey¹⁵ fed rabbits with meat juices, egg albumin and milk, and no changes occurred. He then fed rabbits with egg yolk, and a fatty infiltration of the intima developed. He said that the changes were similar to those found in human arteriosclerosis. Stuckey tried many different animal and vegetable fats but no intimal changes occurred in the aorta, except in those fed with egg yolk and brain substance. Anitschkow and Chaladow,¹⁶ after feeding brain substance and egg yolk to rabbits, recognized that the lipid deposits in the intima doubly refracted polarized light and concluded that the fatty deposits were cholesterol esters. They then fed pure cholesterol and produced a hypercholesterolemia and found lipid deposits in nearly all of the parenchymatous organs of the body. In 1924, Anitschkow,¹⁷ in an article summarizing his work on this subject, stated that the hypercholesterolemia was the main factor in development of arteriosclerosis. He observed that in experimental work in internal parenchymatous organs, a universal deposit of lipoids occurred, while in the human being only the larger vessels had lipoids in their walls; and furthermore, that an extensive hypercholesterolemia must be present to cause lipid deposits experimentally, while in human beings extensive lipid deposits form without a high degree of hypercholesterolemia. Anitschkow attempted to produce a selective lipid deposit in the aorta without much deposit in the liver, kidney and other organs. The results were as follows: (1) the arteriosclerotic changes were hastened when the hypercholesterolemia

13. Joslin, Elliott P.: The Ten-Year Diabetic. What He Is. What He Should Be. How to Make Him So, *Am. J. M. Sc.* **175**:472, 1928.

14. Ignatowski, A.: Zur Frage ueber den Einfluss der animalischer Nahrung auf der Kaninchenorganismus, *Berichte der Kaiserlichen militär-mediz., Akademie zu St. Petersburg*, 1908, p. 16.

15. Stuckey, N. W.: Ueber die Veränderungen der Kaninchenaorta bei der Fütterung mit verschiedenen Fettsorten, *Centralbl. f. Allg. path. u. path. Anat.* **23**:910, 1912.

16. Anitschkow, N., and Chaladow, S.: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Endstehung einiger Pathologischer Prozesse. *Centralbl. f. Allg. path. u. path. Anat.* **24**:1, 1913.

17. Anitschkow, N.: Zür Aetiology der Atherosklerose. *Virchows Arch. f. path. Anat.* **249**:73, 1924.

posterior roots were divided for relief from pain. Three weeks later, he developed pleurisy on the left side of the chest with painful respiration and elevation of temperature. The observation on the chest showed a pleural effusion, but on aspiration fluid was not obtained. The patient was readmitted to the Montefiore Hospital in October, at which time he received applications of deep roentgen and radium therapy without any benefit. He died on October 24.

Diagnosis.—The diagnosis was lymphosarcoma with metastases to various organs and the vertebral column.

In this case the mass was chiefly confined to the chest, with later involvement of the cervical lymph nodes. The diagnosis of lymphosarcoma was arrived at clinically. Autopsy was not done. The neurologic signs, especially the excruciating pains, were due to metastasis to the vertebrae which caused pressure on the roots. The administration of deep roentgen or radium therapy failed to alleviate the symptoms.

CASE 7.—L. S., a woman, aged 38, was admitted to the Montefiore Hospital on Nov. 14, 1922. In March, 1922, she had noticed a painless but annoying swelling of the left tonsil. Tonsillectomy was done in April, followed a week later by a swollen gland in the left submaxillary region. In August, a tumor, the size of a hen's egg, was removed below the left ear. A month later, the swelling became markedly enlarged causing dysphagia. Following the administration of radium combined with deep roentgen therapy, a slight improvement was noticed. In November, there was a recurrence of the swelling and of the symptoms with severe pains radiating from the left side of the neck down to the arm. In the interim, she lost 25 pounds (11.3 Kg.).

The past history was unimportant.

Examination.—Physical examination showed the patient to be fairly well nourished with a tremendous swelling of the left side of the face, extending posteriorly below the concha and occiput into the spines of the cervical vertebrae, with a subjective sensation of choking, inspiratory stridor and nasal speech. The left eye could not be closed completely; the mouth could not be opened for a distance greater than 1 cm., and the tongue could not be protruded. The heart, lungs and abdomen were normal. Two small draining sinuses were present. The left clavicle could not be palpated.

Neurologic examination revealed a left peripheral facial paresis with a questionable paresis of the left fifth motor nerve. There were apparently no sensory disturbances. The left upper extremity was extremely tender and could not be moved. The left biceps and triceps reflexes were absent. All other reflexes were normal.

Laboratory Observations.—The urine was positive for albumin, with many red and white blood cells. A biopsy at the Memorial Hospital showed the mass to be a lymphosarcoma. The roentgenogram showed evidences of metastases in the lower dorsal spine. All other laboratory data were negative.

Course.—The patient was in the hospital for only four days, during which time she received one treatment with radium without any benefit. She developed dyspnea and cyanosis and died on November 19.

Diagnosis.—The diagnosis was lymphosarcoma of the neck.

The only neurologic sign presented in this case was a peripheral involvement of the left facial nerve with a questionable involvement of

was combined with some mechanical or toxic factors; (2) animals (rabbits) fed on small doses of cholesterol for two and one-half years developed no hypercholesterolemia, but a moderate degree of arteriosclerosis was found and the other organs were normal. He stated that lipoids were deposited where the intima was damaged, and that an abnormal cholesterol metabolism plus some strain (mechanical or toxic) brought on arteriosclerosis.

Aschoff¹⁸ differentiated between the atherosclerosis seen in the ascending, the summit, and the descending periods in the life of a vessel. The ascending period in the life of the vessel ends with the thirty-second year; the summit is from then until the forty-fifth year, which marks the commencement of the descending period. In discussing the atheromatosis of puberty, he emphasized that the essential factors in this early form are a swelling of the inner layers of the intima, with a diffuse minute granular deposition of fat beginning in the depths of the stria elastica terminalis, and extending further and further toward the surface. Aschoff stated that the atheromatous spots develop in the regions of the vascular system which are under great physiologic strain. He added that there is a second factor that must be present before the atheromatous spots may appear. This, he said, is a sufficient concentration of lipoids, especially cholesterol esters, in the plasma. From a plasma of low concentration of cholesterol no deposition of lipoids will occur, even though mechanical conditions are favorable.

In the case reported here, the forces necessary for the production of lipid deposits were present. To what extent the various factors, such as the infections and hypertension, influenced the lipid changes is difficult to state. The arteriosclerosis and lipid deposits in the aorta and the kidneys appear to have developed independently of the hypertension.

The Arteriolar Changes.—The morphologic changes in the arterioles of the parenchymatous organs have been studied extensively in recent years. Lohlein¹⁹ concluded that arteriolar disease in the secondary contracted kidney may be present, but at times may be absent. He stated that two types of changes may be seen in the afferent glomerular arteriole. First, a dilatation with thinning of the vessel may result from degeneration and necrosis of the arteriolar wall. The necrosis may extend into the loops of the glomerulus leading to an infarction of those loops. Second, hyaline rings may form in the wall of the interlobular artery as well as the afferent arteriole. This hyaline process is associated with a lakelike dilatation of the vessel, usually near the hilum of

18. Aschoff, Ludwig: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924.

19. Lohlein, M.: *Ueber Schrumpfnieren*, *Beitr. z. path. Anat. u. Allg. Path.* 63:57, 1916.

The origin of abdominal bands or disseminated adhesions is frequently unexplained until a careful history yields evidence of a previous ulcer which has probably long since perforated and sealed spontaneously. One of the most instructive cases of this type was seen at autopsy at the Cook County Hospital, in 1928, by Dr. H. G. Wells, who found in a patient with ascites which was clinically attributed to atrophic cirrhosis, fibrous adhesions, the result of a previous perforated ulcer compressing the portal vein.



Fig. 1 (case 8).—A constant, rigid deformity of the prepyloric area due to adhesions following perforation with spontaneous healing.

CASE 6.—L. S., a white man, aged 21, with an antecedent history of ulcer of fifteen months' duration, was operated on, Dec. 15, 1928. In addition to a duodenal lesion, fibrous adhesions throughout the abdomen, most numerous about the duodenum, were found. A previous perforation was suspected, and the patient interrogated accordingly. It was then learned that on May 6, while on a streetcar, he was seized with an intolerable pain which practically annihilated him and caused him to fall from his seat. He was rushed home in a taxicab. Two hypodermic injections were required before the pain moderated. After the second day, the severe pain subsided. After nine days of confinement, the patient resumed his activities. The details of the acute attack were characteristic of a perforated ulcer.

the tuft. When the changes are severe, according to Lohlein, a thrombus may develop leading to a hemorrhagic infarct in the glomerulus.

Branch and Linder²⁰ reported observations on the microscopic examination of the vessels of the kidney and other organs in ten cases of chronic nephritis. Three cases were in children of 3 years, whose parenchymatous organs showed no arteriolar change. In one case,

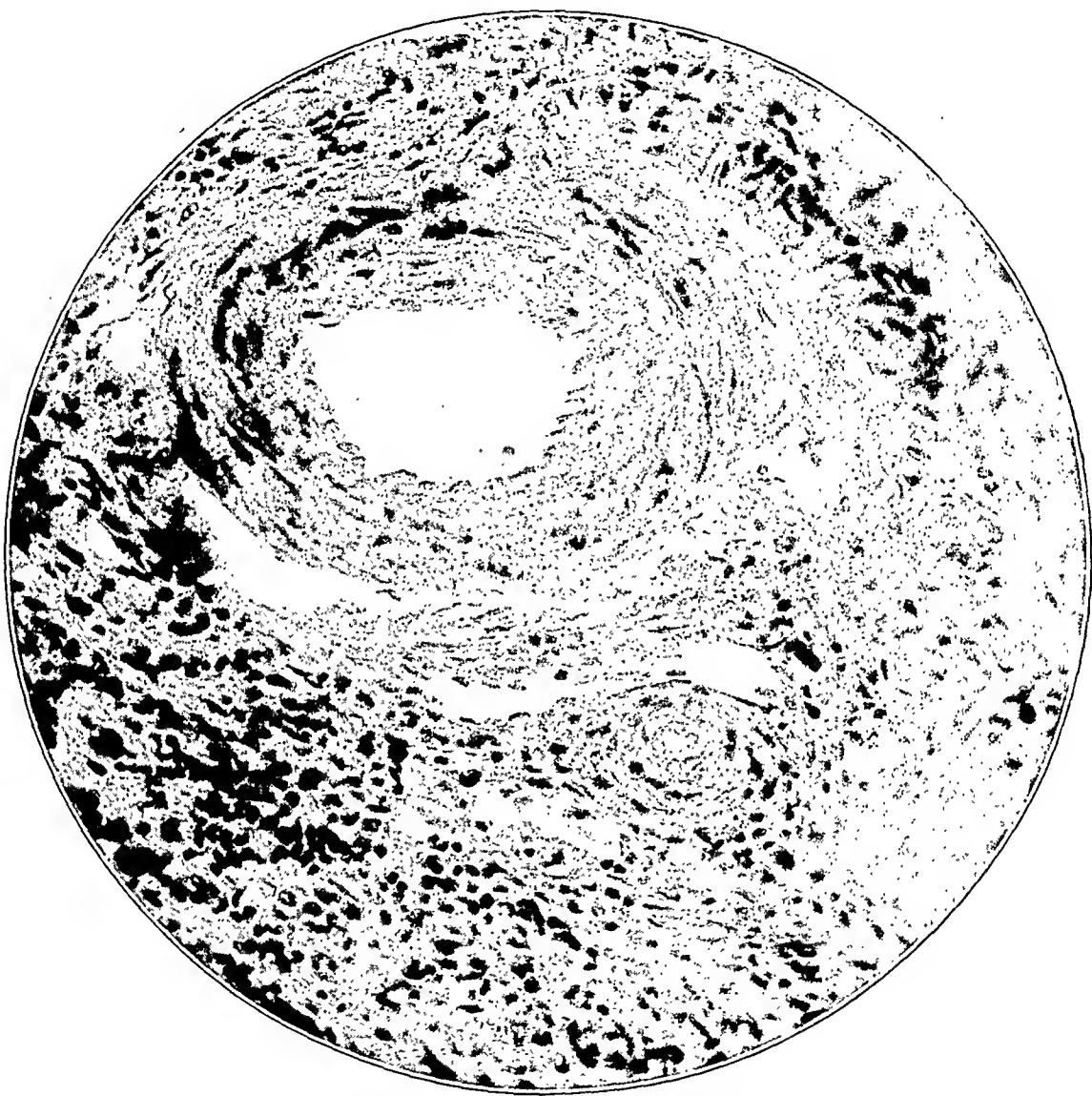


Fig. 4.—A section of kidney showing proliferative changes in the intima of a smaller artery and arteriole; $\times 700$.

nephritis had existed for months but no arteriolar thickening occurred. In the six remaining cases, the arterioles and their parent arteries of the parenchymatous organs were thickened, and the intima had undergone

20. Branch, Arnold; and Linder, Geoffrey C.: The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, *J. Clin. Investigation* 3:299, 1926.

CASE 12.—J. N., a robust white man, aged 71, entered the hospital on Feb. 12, 1929, and related that he had suffered periodically from an ulcerous type of distress since the age of 21. Ten days prior to entrance, he experienced a sharp pain in the upper abdominal region described as resembling the thrust of a dagger. The pain continued to be severe for twelve hours in spite of medication. Vomiting occurred repeatedly. Hiccup began fifteen minutes after the onset of the pain, and was the presenting complaint at the time of admission. Physically, a palpable and audible rub could be detected over the lower right costal region. There was

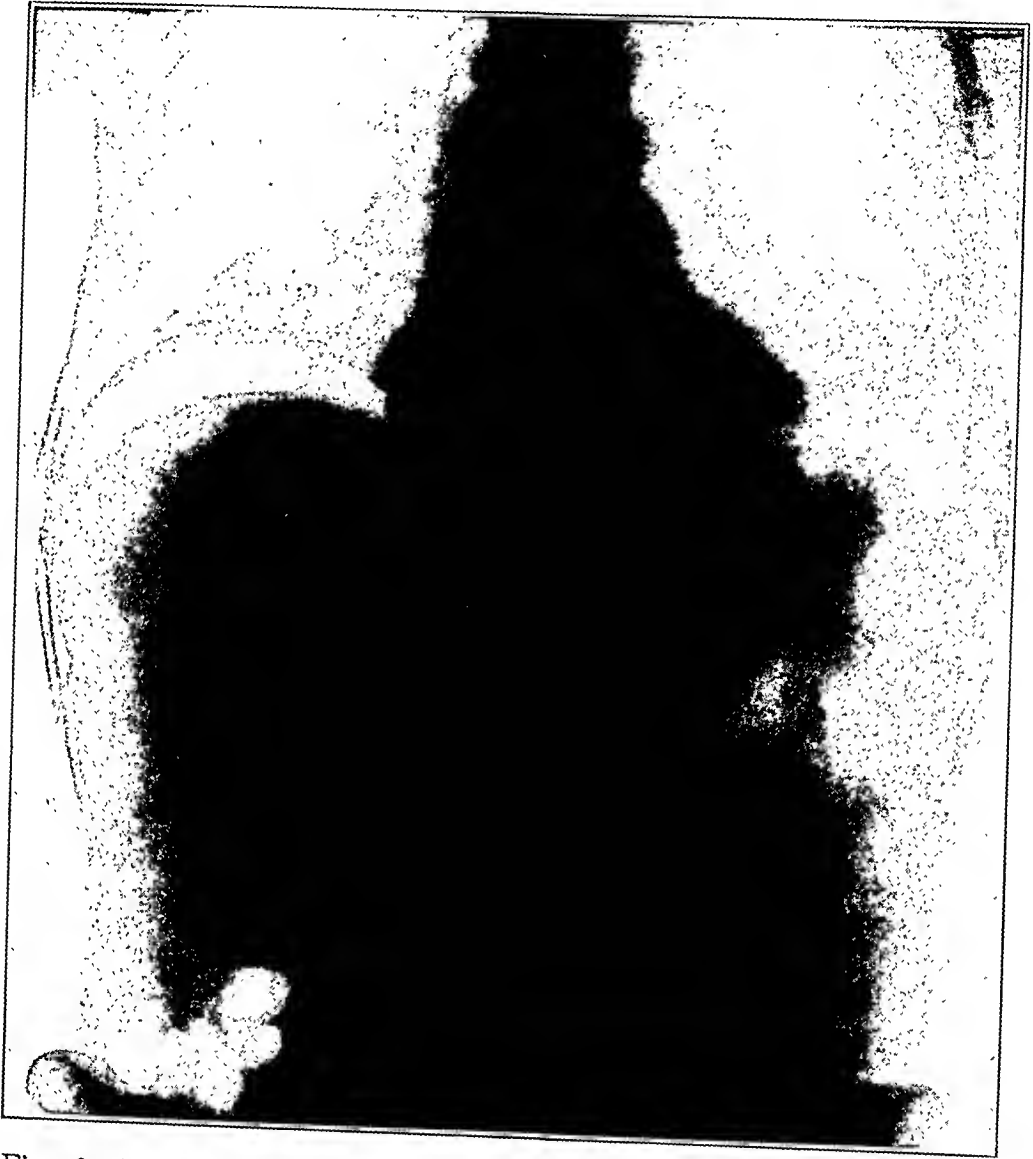


Fig. 3 (case 14).—Pneumoperitoneum from ruptured peptic ulcer which occurred seven days prior to the time the roentgenogram was taken. The gas has accumulated beneath both domes of the diaphragm. Operation was not performed.

a shifting zone of tympany over the normal area of liver dulness. Physical signs of basal compression of the right lung and downward displacement of the liver were obtained. A diagnosis of pneumoperitoneum following perforated ulcer was made. The presence of air was subsequently demonstrated fluoroscopically and a defect of the duodenal bulb visualized in barium studies. The patient was discharged free from symptoms after roentgen examination showed an absence of free intraperitoneal gas.

iatty degeneration and the media was thinned. The authors stated that the arterioles of skeletal muscles were unaffected.

Fishberg²¹ found that the arteriolar lesions of glomerulonephritis were of four histologically and pathologically distinct varieties:

1. Acute necrotizing arteritis was found in patients dying of acute diffuse glomerulonephritis.



Fig. 5.—Unstained section observed under crossed Nicol's prisms, illustrating the doubly refracting nature of the lipoid deposits; $\times 800$.

2. Endarteritis obliterans was present in seventeen of twenty-nine cases of chronic diffuse glomerulonephritis.

3. Arteriosclerosis, similar in histology and distribution of the lesions to that found in essential hypertension, was present in twelve cases of secondary contracted kidney.

21. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, *Arch. Int. Med.* **40**:80 (July) 1927.

CASE 14.—G. B., a colored man, aged 45, who had suffered from epigastric distress for twenty-five years, was admitted to the hospital on May 8, 1929, three days after the onset of excruciating abdominal pain. The intense initial pain subsided during the first twenty-four hours but recurred on the third day of illness. The physical signs at entrance were those of more or less diffuse peritonitis, pneumoperitoneum and bilateral compression of the bases of both lungs. A ruptured peptic ulcer was diagnosed. On May 9, the roentgen examination disclosed the presence of gas under both domes of the diaphragm. A series of subsequent roentgen examinations demonstrated a gradual spontaneous disappearance of the air (figs. 3 and 4). On May 25, a roentgen study with barium revealed a penetrating ulcer on the lesser curvature of the duodenum. The patient left the hospital fully recovered.

CASE 15.—J. S., a tall, slender, white youth, aged 20, was admitted to the hospital on July 4, 1929, with the following history: Since the age of 12 he had suffered from periodic epigastric distress of a mild nature. Three days prior to his acute illness, his previous distress became notably aggravated. On July 1, while sitting, he suddenly felt himself "tied in a knot." The severe pain of onset was transformed to a dull ache following hypodermic injections. Vomiting occurred with each attempt at ingestion. The clinical picture at entrance was that of a diffuse peritonitis with high grade meteorism. Although the diagnosis of a perforated ulcer was made clinically, surgical intervention was deemed inadvisable at that time, which was the fourth day of the acute illness. A roentgenogram made on July 5 showed free air beneath both domes of the diaphragm, considerable gas in the colon and a limited quantity in the small intestine (fig. 5). The evidences of infection gradually subsided spontaneously. By July 12, the free gas was practically entirely absorbed but the splenic flexure remained distended (fig. 6). The patient was ambulatory on the sixteenth and fully recovered on the twenty-third day following the onset of the perforation.

GROUP 4: CLINICAL EVIDENCE OF PERFORATION WITH ROENTGEN INDICATIONS OF ULCER

This group comprises those cases in which convincing testimony is lacking as direct evidence of a perforation either operative or roentgenologic is wanting. There is in each case a history of chronic ulcer distress, usually prodromes of perforation, and those symptoms and signs which characterize a perforative peritonitis. There is also evidence of ulcer or ulcer deformity in the barium meal study made an interval after the assumed perforation occurred. The justification for considering these cases as examples of spontaneous recovery is that clinically they differ in no essential way from those cases corroborated by operation or by the finding of a pneumoperitoneum.

In connection with this group of cases, it is interesting to analyze the report of Kudlek,¹⁸ who aside from Vaughan and Brams²³ and Vaughan and myself²⁴ appears to be the only one who has published

23. Vaughan, R. T., and Brams, W. A.: Roentgen Ray in the Diagnosis of Perforated Peptic Ulcer, *Surg. Gynec. Obst.* **50**:10, 1930.

24. Vaughan, R. T., and Singer, H. A.: The Value of Radiology in the Diagnosis of Perforated Peptic Ulcer, *Surg. Gynec. Obst.* **49**:593, 1929.

4. Muscular hypertrophy in the media of renal arterioles was well marked in many cases of chronic glomerulonephritis.

He stated that the arterioles of the skeletal muscle and skin are usually unimpaired. In his study he found these various morphologic changes at times in the same kidney, and he attributed them to the action of different forces. He concluded that the degenerative or arteriosclerotic changes were dependent on the hypertension, while the endarteritis obliterans, he assumed, was produced by the blocking of the blood flow subsequent to glomerular inflammation.

The arteriolar changes in the case reported here were limited to a large extent to the kidney. While there were a few evidences of arteriolar damage in the liver, the arterioles of the spleen, heart muscle and skeletal muscle appeared normal. No dilatation of the afferent glomerular arterioles could be found, and no hyaline necroses were present. The renal arterioles presented two definite and different forms of disease. First, there was intimal thickening with profound fatty degeneration in connection with an atrophic media, the condition that may be called arteriosclerosis. Secondly, in some arterioles, there was a medial hypertrophy and the intima was thickened from connective tissue proliferation, fatty changes being absent. This endarteritis obliterans was also found associated with medial atrophy in some of the smaller arteries and arterioles. Arteriolar damage in the skeletal muscles was looked for carefully, and none was found. It was evident in this case that the disease of the smaller arteries and arterioles was not widespread as was found by Keith²² in cases of malignant hypertension, but was limited entirely to the kidney. Occasionally, the media was found increased when the intima was intact.

SUMMARY

1. The clinical features of a patient, aged 12 years, with chronic glomerulonephritis and lipoid changes in the various organs, are described from the onset of the disease until death five years later. During the course of the disease it is seen that the symptoms were evanescent and varied so much from time to time that the proper interpretation of the clinical picture was difficult in some stages of the disease.

2. Lipoid deposits in the various parenchymatous organs are described, and their relationship to hypercholesterolemia is discussed. The atherosclerosis of the aorta and mitral valve is described and its dependence on hypercholesterolemia is pointed out.

22. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: The Syndrome of Malignant Hypertension, *Arch. Int. Med.* **41**:141 (Feb.) 1928.

ently takes for granted that the reader concedes him the ability which he feels he possesses to recognize even the less typical cases because of his experience with similar cases checked by operation or by roentgenograms.

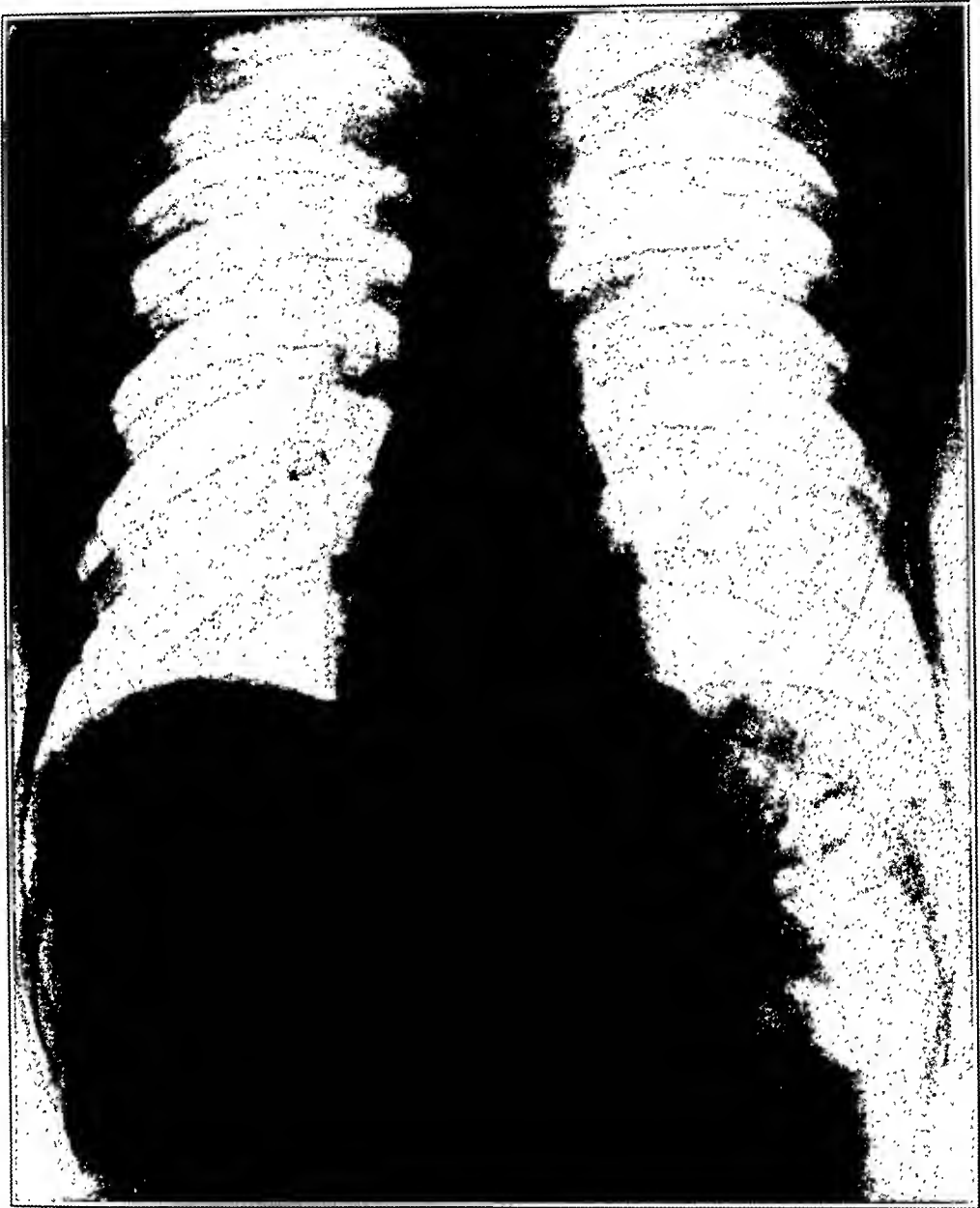


Fig. 6 (case 15).—Appearance of the x-ray film seven days after figure 5 was taken and twelve days after perforation. The free air has been almost completely absorbed. The splenic flexure remains distended by gas.

Particular care has been exercised to exclude those cases in which the severe pain is not due to perforation but to penetration of an ulcer into an adjacent structure. Here, as a rule, the pain is relieved by emptying the stomach or by the ingestion of large doses of alkali. Furthermore, the symptoms and signs of peritonitis are absent or at

3. A description is given of the changes found in the arteries and arterioles of the kidney and other parenchymatous organs as well as those found in the skeletal muscles. The damage found in the renal arterioles is especially dwelt on.

The paintings and photographs that illustrate this paper were done by Mr. Leo Carl Massopust, artist at Marquette University School of Medicine.

CASE 19.—L. K., a tall, thin, white man, aged 25, was admitted to the hospital on July 21, 1929, with exquisite tenderness and clearcut rigidity in the epigastric and right hypochondriac regions. Gallbladder disease was originally diagnosed. Pertinent questions yielded the information that the patient had suffered from an ulcer syndrome which became particularly troublesome two days prior to entrance. On the day of admission, three and a half hours after a meal of cabbage and ham with vinegar, the patient experienced an atrocious epigastric pain which caused him to double up and to squirm about in bed. A private physician advised hospitalization. The patient was admitted four hours after the onset of severe pain. Several injections of morphine were required during the first forty-eight hours. The highest recorded temperature was 100.2 F. For a time, the act of micturition was associated with pain. On July 24, all the symptoms had disappeared and regular Sippy treatment for ulcer was instituted. Roentgen examination showed a general deformity of the bulb. The Graham-Cole test led to normal visualization of the gallbladder. The patient was discharged feeling entirely well.

CASE 20.—C. H., a white man, aged 70, entered the Cook County Hospital for a second time on Sept. 29, 1929. From the record of his first admission, it was learned that he was operated on for a perforated duodenal ulcer on Jan. 25, 1925. The hole was sutured, and a posterior gastro-enterostomy was performed. Following recovery from the operation, distress appeared only after dietary indiscretions. On Sept. 26, 1929, while on a streetcar, the patient was seized without warning by an extremely agonizing pain which caused him to scream and to fall from his seat. He was taken home in an automobile and treated by a private physician. The patient said that the abdomen was as "hard as stone." After twenty-four hours, the severe pain began to subside. Except for slight tenderness in the epigastrium and on the left side of the upper part of the abdomen, the results of the physical examination were negative. Roentgenographically, there was observed at the gastrojejunal stoma a filling defect, which disappeared after two weeks of ulcer management. The patient was discharged fully recovered presumably from a perforated gastrojejunal ulcer.

COMMENT

The general view with regard to the uniformity of the clinical course and the ease of diagnosis of ulcer perforations is summed up in the statement, "Perforation of the stomach into the general abdominal cavity is a catastrophe so sudden, so rapid and definite in its progress that it is generally recognized without difficulty." From a study of the foregoing case reports, however, one does not gain this impression. In the first place, the course of the disease appears quite variable and by no means uniformly progressive. Many of the cases indicate that following the initial severe manifestations of onset, instead of progression there is more or less rapid subsidence of symptoms and recovery. These are cases in which early closure of the perforation occurs and in which the amount of leakage from the stomach or duodenum is limited. The mildness of the clinical manifestations following onset led Vaughan²⁵ and myself to choose the term "formes frustes" with

25. Singer, H. A., and Vaughan, R. T.: The "Formes Frustes" Type of Perforated Peptic Ulcer. *Surg. Gynec. Obst.* 50:10, 1930.

HEMOCHROMATOSIS

REPORT OF A CASE, WITH STUDIES OF THE COPPER CONTENT
OF THE LIVER *

ELMER H. FUNK, M.D.

AND

HUSTON ST. CLAIR, M.D.

PHILADELPHIA

In 1889, von Recklinghausen described a form of pigmentation affecting many organs of the body which he called hemochromatosis. This condition is often accompanied in its terminal stages by diabetes—the bronze diabetes of French writers. While the number of recorded cases (approximately a few over 100) would indicate that the condition is rare, various observers have pointed out that it may easily be overlooked clinically in the early stages when the skin pigmentation, glycosuria and the hemosiderin granules in the urine are absent. Mills¹ reported that in seventeen pathologically advanced cases, only two were recognized during life and proved positive by the demonstration of hemosiderin in an excised piece of skin. Many patients, no doubt, die of intercurrent diseases before the positive clinical picture of hemochromatosis is established. Excellent pathologic and clinical studies are recorded in the literature. The characteristic pathologic picture is the presence of hemofuscin and hemosiderin in the cirrhotic liver, the pancreas, their regional lymph nodes and various other organs and tissues. Blanton and Healy,² in an analysis of fifty-three cases, noted that clinically the liver was found to be enlarged in most instances, markedly in 4 per cent, moderately in 10 per cent, slightly in 60 per cent, and not enlarged in 20 per cent. At necropsy, 95 per cent were recorded as enlarged. Ascites occurred in about one third of the cases. Glycosuria was present in 85 per cent of the cases with a record of such a study (average sugar content, 5 per cent). The spleen was more often not enlarged than otherwise on clinical examination. Among

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* Read before the Association of American Physicians, Atlantic City, N. J., May 7, 1929.

* From the Medical Service of Dr. Thomas McCrae and the Ayer Clinical Laboratory of the Pennsylvania Hospital.

1. Mills, E. S.: Hemochromatosis with Special Reference to Its Frequency and to Its Occurrence in Women, *Arch. Int. Med.* **34**:292 (Sept.) 1924.

2. Blanton, W. D., and Healy, W.: Hemochromatosis: Report of Four Cases, *Arch. Int. Med.* **27**:406 (April) 1921.

instance, *caeteris paribus*, if a patient said that he experienced "an extremely agonizing and most intolerable" pain but nevertheless completed his day's work and sought no measures for relief, the diagnosis of perforation is less likely than when he asserts that he felt merely a "hard" pain, ceased work instantaneously and summoned medical aid immediately. The reader may have been struck by what appeared to him unnecessary details in the recorded case histories regarding activities of patients just prior to and after onset. These seemingly irrelevant items, however, will be found to furnish the physician with far better material on which to base a conclusion than the patient's subjective description of his complaints.

The question naturally arises as to how frequently spontaneous recovery would ensue if all patients with perforated ulcers were treated without surgical measures. The attempt to arrive at a trustworthy answer is beset with many difficulties. In the first place, since operation is performed in practically all cases of perforated ulcer which are recognized within the first twenty-four hours or so, it is difficult to estimate how many of these would have resulted in spontaneous closure if the surgeon had not intervened. In the second place, it is almost impossible to judge how many abortive or mild cases fail to come under medical observation, to say nothing of the number which are unrecognized when patients come under the observation of physicians. Thirdly, when the diagnosis is not checked by operation or by the presence of free air, there is always a possibility of error which must be taken into account.

In the absence of more accurate data, an estimate based on the foregoing study may be warranted at this time. During the period of observation, there were just as many cases of spontaneous recovery in patients treated in the hospital as there were perforations with continuous leakage. Based on this observation and on impression, it is estimated that the chances for recovery from perforation of a peptic ulcer into the free abdominal cavity is no less than 50 per cent; in other words, instead of constituting an almost invariably lethal complication of ulcer, perforation without operation is followed by recovery in at least one half of the total number of cases.

Because the statement is made that spontaneous recovery frequently occurs, it should not be assumed that conservative management is recommended. The possible bearing which the incidence of recovery without laparotomy has on present methods of treatment is not considered in this article. The object of the paper is merely to correct what appears to be a general misconception in regard to the outcome of perforations that are not handled surgically, and to throw light on a number of what were hitherto diagnostic problems and obscure phenomena.

3. A description is given of the changes found in the arteries and arterioles of the kidney and other parenchymatous organs as well as those found in the skeletal muscles. The damage found in the renal arterioles is especially dwelt on.

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ever, in the mild and abortive types and in cases seen after the symptoms of onset have subsided, an incorrect diagnosis is generally made in a majority of instances.

The important points in the detection of many of the cases of spontaneous recovery are: (1) the knowledge that their occurrence is not uncommon, (2) a thorough acquaintance with the manifestations of the less typical perforations and (3) a careful and detailed minute to minute history. The history includes not only the subjective complaints of the patient, but also his actions and reactions in response to these symptoms.

Although accurate statistics cannot be offered on account of the inherent difficulties that stand in the way of a correct analysis, it is believed that spontaneous recovery occurs far more frequently than has hitherto been supposed. It is estimated that in a large series of cases of perforated ulcer in which surgical closure is not performed at least 50 per cent will recover.

The observation that spontaneous recovery from perforated peptic ulcer is a common occurrence is offered as a statement of fact which may aid in diagnosis and serve to elucidate a number of obscure clinical problems and statistical paradoxes. No conclusions are drawn in the article regarding the bearing which this observation might have on the present methods of treatment for perforated ulcer. No statement is made which contradicts the current belief that in general perforated ulcer constitutes a surgical emergency.

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forty-eight patients 31 per cent had slightly, 4 per cent moderately, and 4 per cent considerably, enlarged spleens; in 61 per cent the spleen was not palpable. At necropsy the abdominal lymph glands, as a rule, are firm and show massive collections of iron pigment, giving a gross appearance varying from brown to a chocolate color. The skin pigmentation occurs in about half of the cases, but microscopic studies of the skin show a wide disparity between the clinical appearances and the postmortem observations.

REPORT OF CASE

History.—A white man, aged 44, a construction iron worker, was admitted to the Pennsylvania Hospital, Oct. 2, 1928, and died, Oct. 26, 1928. The chief complaints were discoloration of the skin, weakness, enlargement of the abdomen and "yellow" stools. The patient stated that he had always been in good health prior to the present illness, except for gonorrhea at the age of 16. For many years he had used alcohol excessively, but none during the six months prior to admission. He had used no drugs. The onset of the present illness was dated to August, 1927, when he noted a change in the color of the skin. He felt well, however, until January, 1928, when the abdomen began to enlarge and the stools became clay-colored. Attacks of diarrhea occurred about once a week. Since the onset a loss of 20 pounds (9 Kg.) in weight occurred, with an insidious weakness which became progressively worse until he was compelled to stop working about six weeks before admission.

Physical Examination.—On admission, the patient was fairly well nourished; the face presented a curious discoloration somewhat suggestive of argyria. The neck and arms were brownish and suggested pigmentation due to exposure to the sun. The skin of the covered parts was "bronzed." The sclerae were icteric. There was no generalized lymphadenopathy. The tongue was coated, the breath offensive and pyorrhea alveolaris marked. Examination of the lungs showed nothing abnormal. The heart was enlarged, the cardiac sounds were clearly heard, and a soft systolic murmur was heard at the apex. The abdomen was distended, especially in the upper part. The liver was distinctly enlarged and felt irregular, but was not tender and the liver border was located about 10 cm. below the costal margin in the right midclavicular line. The spleen was easily felt and apparently touched the left lobe of the liver. There was distinct flatness in the flanks suggesting moderate ascites. The external genitals, the rectal examination and the extremities showed nothing of note. The temperature was normal, the pulse rate was 90, and the blood pressure was 110 systolic, 68 diastolic.

Laboratory Studies.—A small section of skin removed from the inner side of the forearm showed histologically the iron pigmentation characteristic of hemochromatosis.

The urine gave a positive Rous test for hemosiderin but was otherwise normal.

Studies of the blood showed a moderate secondary anemia, a sugar content of 105 mg. per hundred cubic centimeters and a urea nitrogen content of 16 mg. per hundred cubic centimeters, negative Wassermann and Kahn reactions and an immediate direct van den Bergh reaction with 3 mg. of bilirubin (6 units) per hundred cubic centimeters of blood.

The stools were semisolid and clay-colored, and bile was absent.

According to the bromsulphalein test (2 mg. per kilogram of body weight), there was impairment of liver function as 22 per cent of the dye remained in the blood after thirty minutes.

The fractional gastric analysis showed hypo-acidity, and biliary drainage revealed a greenish yellow bile which on culture was found to be sterile.

Clinical Course.—Temporary improvement in strength occurred during the first two weeks after admission, then cough, fever, dyspnea, cyanosis, increasing distention of the abdomen, increasing jaundice and progressive weakness rapidly followed each other and coma and death occurred. The last examination revealed the signs of pneumonia, increased fluid in the abdomen, and a terminal phlebitis and cellulitis of the right leg. The blood culture at the time showed a pure growth of the colon bacillus.

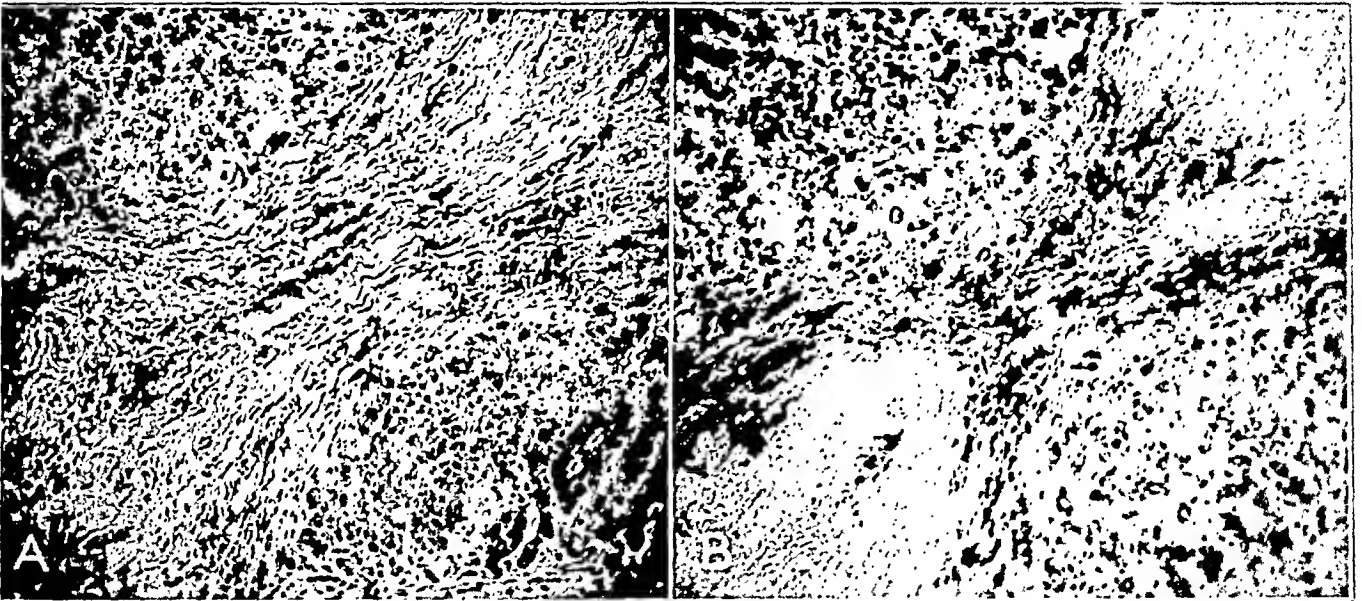


Fig. 1.—*A*, low power magnification of liver showing fibrosis and proliferation of bile ducts. Hematoxylin-eosin stain. *B*, same area stained for iron showing massive deposits in parenchymatous cells, especially those bordering the area of fibrosis.

Necropsy Studies.—The necropsy observations are in agreement with the excellent descriptions of Abbott, Opie, Sprunt, Mallory and others. Briefly, they are as follows:

The general appearance has been described. Permission could not be obtained for examination of the brain and spinal cord. The only macroscopic lesion in the thoracic cavity was bronchopneumonia. The liver, spleen and pancreas and their regional lymph nodes were enlarged and firm. There was approximately 1 liter of straw-colored, serous fluid in the peritoneal cavity.

The liver weighed 2,370 Gm. The surface was irregular but not nodular as in atrophic cirrhosis. On section, the cut surface was ochre-colored, with countless plainly visible interlacing bands of fibrous tissue. The pancreas was a dirty yellow and was markedly fibrosed. Both organs contained irregularly distributed, numerous, fine, dark green streaks.

The spleen weighed 670 Gm. It was dark red and firm with moderate prominence of the vessels and trabeculae. The capsule was thickened and opaque.

The mesenteric lymph nodes draining the liver, spleen and pancreas were dark brown, in contrast to the smaller, pale, edematous lymph nodes in the lower part of the abdomen.

No gross lesions of interest were found in the suprarenals, kidneys, bladder or elsewhere.

Microscopically, large deposits of hemofuscin and hemosiderin were found in the liver, pancreas, splenic capsule and their regional lymph nodes. Lesser deposits were found in the splenic parenchyma, suprarenals, heart and skin. Traces were found in almost any section of any organ. There was a tendency for the pigment to lie within the parenchymatous cells. Thus, in the liver (fig. 1), the Kupffer and liver cells contained practically all the deposits; in the pancreas (fig. 2), the acinar cells and the cells of the islands of Langerhans; in the heart, the muscle fibers; in the suprarenals (fig. 3), the cells of the zona glomerulosa,

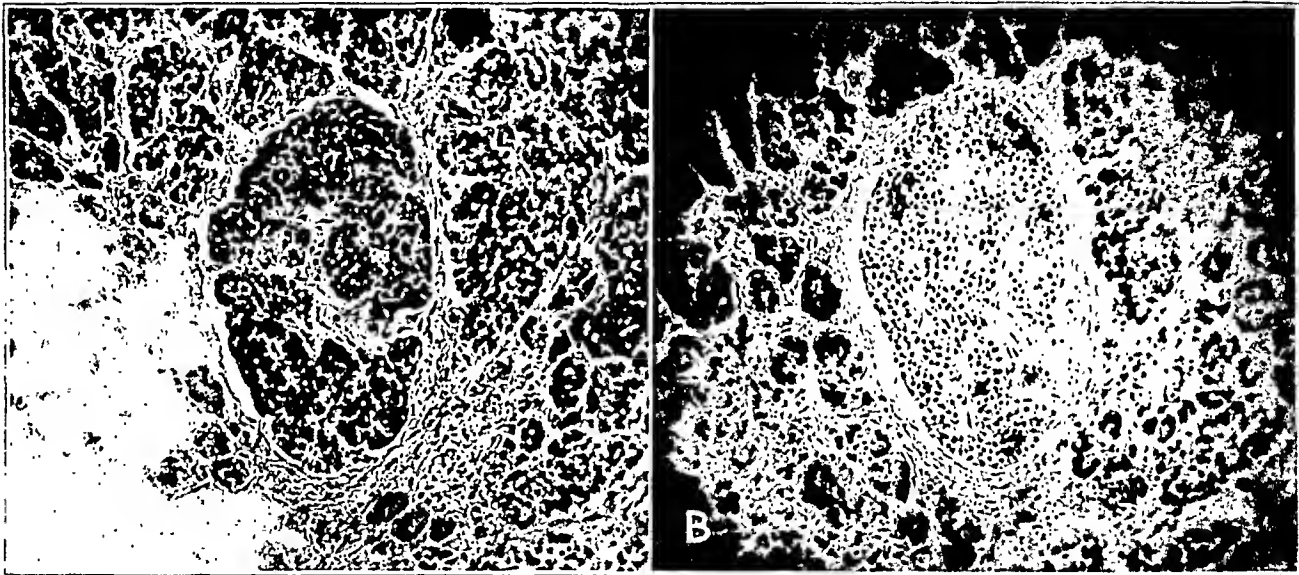


Fig. 2.—*A*, high power magnification of pancreas showing island of Langerhans and surrounding acini infiltrated with fibrous tissue. Hematoxylin-eosin stain. *B*, same areas stained for iron showing deposits in the acinar cells and to a less degree in the islet cells.

and in the lungs, the epithelial cells of the mucous glands of the bronchi. Minute deposits only were found in fibrous tissue. Traces were seen in some of the cells of the tubular epithelium in the kidneys and in the stroma of the tunica propria of the intestines.

In addition to the iron pigment, another pigment which we believe is melanin was found in the skin.

Chemical Studies.—Analyses of the tissues for copper were made by the method reported by Rose and Bodansky.³

The tissue was ground, treated with sulphuric acid, charred, treated with nitric acid and then ashed. The ash was extracted with hydrochloric acid and

3. Rose, C., and Bodansky, M.: Biochemical Studies on Marine Organisms, *J. Biol. Chem.* **44**:99, 1920.

the iron removed with hydrogen sulphide, after which the copper was estimated colorimetrically. Our percentage of error was determined to be between 5 and 6 per cent, approximately the same as that found by Rose and Bodansky.

We found 140 mg. of copper per kilogram of fresh liver tissue and estimated the total copper content of the liver to be 331.8 mg.

In the spleen, there was less than 0.1 mg. per hundred grams of tissue, and therefore less than 1 mg. in the entire spleen.

As controls, two livers without pigment cirrhosis were analyzed. One contained less than 1 mg. of copper per kilogram of tissue and the other 9 mg. of copper per kilogram of fresh tissue.

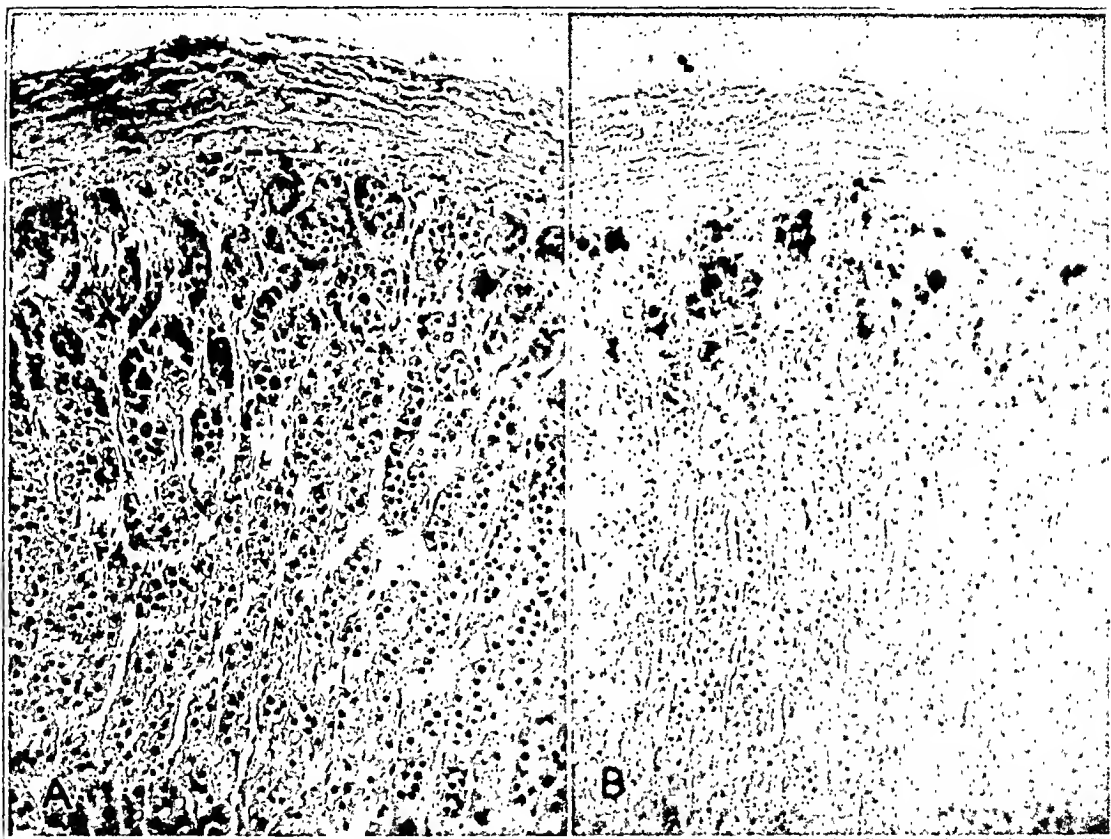


Fig. 3.—*A*, high power magnification of suprarenal gland, showing increased pigmentation in zona glomerulosa of the cortex due, as indicated by *B*, to iron pigment.

The estimate of the iron content was probably inaccurate, as the liver had been kept in Klotz's solution for several weeks before analysis. We used Kennedy's⁴ method of digesting the organic matter in a mixture of perchloric and sulphuric acids, then treating it with a solution of sodium sulphocyanate and extracting the resulting ferric salt with amyl alcohol. This alcoholic solution was compared in a colorimeter with a standard iron solution.

The iron content of the liver was estimated to be 6.2 Gm. per kilogram of tissue, the entire liver, on this basis, containing 14.7 Gm. of iron.

The results of analyses of human organs for copper and some of the figures for iron are shown in tables 1 and 2.

4. Kennedy, R. P.: The Quantitative Determination of Iron in Tissues, *J. Biol. Chem.* **74**:385, 1927.

COMMENT

The cause of the excessive deposition of iron is not known. In the past few years, Mallory⁵ has suggested that copper may be the primary etiologic factor in hemochromatosis. He divided nineteen patients into three groups: (1) those giving an alcoholic history, seven cases; (2) those who had occupational exposure to copper, four cases; (3) those whose histories throw no light on a possible cause, eight cases. Mallory regarded the chief action of copper absorbed in the body as hemolysis of the red blood cells with the liberation of hemoglobin in the circulation. Part of this is eliminated, but any excess is deposited in a

TABLE 1.—*The Copper Content of the Liver and Other Organs in Cases Not Showing Hemochromatosis*

	Organs Examined	Number of Cases	Milligrams of Copper per Kilogram of Tissue	Grams of Iron in Entire Liver	Comment
Flinn and Von Glahn.....	Livers	20	2.30-12.42	...	{Copper workers
	Livers	2	3.74	...	
			5.34	...	
Mallory.....	Livers	4	0.78-20.40	...	
Pennsylvania Hospital.....	Livers	2	1.60 and 9.00	...	
Wells.....	Livers	Normal	0.3	

TABLE 2.—*The Copper Content of the Liver and Other Organs in Cases Showing Hemochromatosis*

	Organs Examined	Number of Cases	Milligrams of Copper per Kilogram of Tissue	Grams of Iron in Entire Liver
Mallory.....	Liver.....	1	1.48
	Bone.....	1	3.12
	Liver and other organs	2	3.52 and 3.56
	Liver and kidney.....	1	19.14
Pennsylvania Hospital....	Spleen.....	1	Trace
	Liver.....	1	140.00	14.7(?)

changed condition as hemofuscin in the liver and other organs. In many kinds of cells, this is broken down with formation of hemosiderin, the whole process leading to necrosis and later sclerosis. Mallory showed experimentally that copper powder is absorbed through the respiratory or gastro-intestinal tracts and that there follows a deposition of yellow pigment, hemofuscin, in the liver, heart, kidneys, bone marrow and probably in other organs. He noted that citric and other acids, so frequently present in foods, are efficient solvents for copper. Copper

5. Mallory, F. B.; Parker, F., and Nye, R. N.: Experimental Pigment Cirrhosis Due to Copper and Its Relation to Hemochromatosis, *J. M. Research* **42**: 461, 1921. Mallory, F. B.: The Relation of Chronic Poisoning with Copper to Hemochromatosis, *Am. J. Path.* **1**:117, 1925; Hemochromatosis and Chronic Poisoning with Copper, *Arch. Int. Med.* **37**:336 (March) 1926.

cooking vessels, water pipes, cocktail shakers, "moonshine" whisky, copper dust in certain occupations, and a number of other possible sources of copper cause every one to be exposed to ingestion of the metal.

More recently, Lindow, Elvehjem and Peterson⁶ determined the copper content of about 160 samples of the common food material. The figures range from 0.1 mg. of copper per kilogram of fresh celery to 44.1 mg. per kilogram of fresh calf liver. The degree of variation in the copper content of foods falling in the same class was less than that of either manganese or iron. A wide distribution of copper in food materials was found, no food examined being without this element.

A small quantity of copper is considered as a normal constituent of various organs and body fluids by McHargue⁷ and by Warburg and Krebs.⁸ The latter found approximately 0.0017 mg. of copper per cubic centimeter of blood and about the same amount associated with the serum proteins. McHargue, analyzing the organs of cattle, found that the liver was the richest in copper; and in this organ the highest amounts were found in early life. The liver of a calf born dead contained 908 mg. of copper per kilogram of dried material, of a calf 5 days old 400 mg. of copper, and of an ox 50 mg. The spleen of the ox contained 16.6 mg. and lean meat 4 mg. per kilogram of dried material.

Supplee and Bellis⁹ and also Quam and Hellwig¹⁰ found that the copper content of milk varied from 0.2 to 0.8 mg. per liter. The amounts were quite constant over four states and without any apparent correlation between diet and the quantity of copper present.

We do not know the effect of feeding copper-free diets over long periods, but we can state that all human beings and many, if not all, other animals ingest copper in varying amounts with each meal.

Hall and Butt¹¹ have obtained experimental results which support the observation that copper salts ingested over long periods of time produce in rabbits a pigment cirrhosis closely resembling the early manifestations of hemochromatosis in man. However, they have shown that alcohol not only fails to hasten or augment the production of pigment

6. Lindow, C. U.; Elvehjem, C. A., and Peterson, W. H.: The Copper Content of Plant and Animal Foods, *J. Biol. Chem.* **82**:465 (May) 1929.

7. McHargue, J. S.: The Association of Copper with Substances Containing the Fat-Soluble A Vitamin, *Am. J. Physiol.* **72**:583, 1925.

8. Warburg, O., and Krebs, H. A.: Loosely Bound Copper and Iron in Blood Serum, *Biochem. Ztschr.* **190**:143, 1927.

9. Supplee, G. C., and Bellis, B.: *J. Dairy Sc.* **5**:455, 1922.

10. Quam, G. N., and Hellwig, A.: The Copper Content of Milk, *J. Biol. Chem.* **78**:681, 1928.

11. Hall, E. M., and Butt, E. M.: Experimental Pigment Cirrhosis Due to Copper Poisoning, *Arch. Path.* **6**:1 (July) 1928.

cirrhosis, but reduces materially the storage of copper in the liver in both rabbits and white rats. They did not accept a factor of increased blood destruction. Hall and Butt, Dunn,¹² Howard and Stevens¹³ and others have submitted evidence that increased hemolysis does not account for the pigment. The chief reasons are: (1) Anemia does not necessarily exist; (2) no tests for hemolysis are positive; (3) there are no signs of activity in the bone marrow and other hemopoietic organs; (4) there is a slow but definite retention of food iron; (5) the distribution of iron in hemochromatosis and in the hemolytic anemias is quite distinct. In hemochromatosis the spleen and bone marrow are pigmented to a slight degree as compared to the liver, pancreas and some other organs. In the hemolytic anemias, the reverse is true. As Rous and Oliver¹⁴ have shown in their experiments with blood transfusions over long periods, the spleen and bone marrow collect hemosiderin to the limit of their capacity, after which the liver begins to be pigmented. Thus, it is unlikely that copper causes hemolysis with a resulting storage of iron.

Some recent studies indicate that copper may play an important part in the normal metabolism of iron. Hart, Steenbock, Waddell and Elvehjem¹⁵ discovered during the course of experimental investigations of the rôle of iron in nutrition that copper may be a factor in the building of hemoglobin in a mammal. Experimentally, in the treatment for anemia in rats they found that liver extract was just as effective as it has been found to be in man, and that this effectiveness could be duplicated by the use of copper alone which is a constituent of the Lilly liver extract which they used. They did not know how copper in the presence of iron and an otherwise satisfactory diet functions in hemoglobin building, especially since copper is not a constituent of hemoglobin. They suggested that copper may act as a catalyzer for some reactions concerned in hemoglobin building just as iron functions in the production of the noniron-containing chlorophyll molecule.

Flinn and Von Glahn¹⁶ conclude from careful feeding experiments on animals with and without the addition of copper to the dietary that:

12. Dunn, J. S.: Hemochromatosis, *Lancet* **2**:334, 1921; *Brit. M. J.* **2**:783 (Nov. 12) 1921.

13. Howard, C. P., and Stevens, F. A.: The Iron Metabolism of Hemochromatosis, *Arch. Int. Med.* **20**:896 (Dec.) 1917.

14. Rous, P., and Oliver, J.: Experimental Hemochromatosis, *J. Exper. Med.* **28**:629, 1918.

15. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Copper as a Supplement to Iron in Hemoglobin Building in the Rat, *J. Biol. Chem.* **77**: 797, 1928.

16. Flinn, F. B., and Von Glahn, W. C.: A Chemical and Pathological Study of the Effects of Copper on the Liver, *J. Exper. Med.* **1**:5, 1929.

"It is apparent that copper is not the cause of the pigment deposits in the liver of the rabbit, since the same change is produced when sodium acetate is given with the standard diet. Furthermore, when rabbits are fed on a diet of carrots exclusively, the deposition of pigment occurs with greater rapidity than with copper or its compounds and the standard diet. The changes resulting in the livers of the carrot-fed animals are identical in every way with those seen following large doses of copper and in animals given comparable doses of sodium acetate." Thus, that which only copper and possibly zinc were supposed to accomplish in pigmentation of the liver is found to occur with the use of sodium acetate or of carrots. How many other combinations can do the same is a matter of pure conjecture.

In hemochromatosis there is a tremendous increase in the quantity of iron in the body, especially in the liver. It seems that there is also an increase in copper. As food iron is retained, might not copper be retained, and zinc, manganese and other substances? We have found no reference to analyses for elements other than iron and copper, although complete analyses including those of zinc, manganese, nickel and bismuth might result in interesting and enlightening data.

CONCLUSIONS

1. A case of hemochromatosis without diabetes is reported.
2. The copper content of the liver was found to be 140 mg. per kilogram of fresh tissue, or 331.8 mg. for the entire organ.
3. The copper content of the spleen was found to be less than 1 mg. for the entire organ.
4. The estimated quantity of iron in the liver is probably inaccurate but was found to be at least 6.2 Gm. per kilogram of tissue or 14.7 Gm. for the entire organ.
5. No analyses were made for zinc, manganese, nickel or other heavy metals.
6. It is unlikely that increased hemolysis is the cause of the iron pigmentation.
7. It is likely that the rôle played by copper is secondary to an unknown etiologic agent.

A COMPARISON OF THE BLOOD SUPPLY OF THE RIGHT AND LEFT VENTRICLES IN CHILDHOOD *

MERRITT B. WHITTEN, M.D.

Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN.

The differences in the blood supply of the right and left ventricles have not been sufficiently emphasized. The reason for this probably lies in the fact that most of the recent contributions to the knowledge concerning the coronary circulation have been acquired from a study of cleared specimens of the heart. These preparations are seldom entirely transparent. Consequently, in the thicker portions, such as the left ventricle, the arterial tree is incompletely shown. The roentgen method also has been used by many observers. This method is likely to give misleading pictures, owing to the fact that the interventricular septum is crescent-shaped, which makes it difficult to distinguish the vessels of the septum from those of the cardiac wall.

On the contrary, specimens prepared by the celluloid corrosion method are better suited for a comparison of the blood supply of the two ventricles. If casts of the cavities of the heart, as well as of the coronary arteries, are made according to the technic that I¹ described recently, the relation of the vessels is fairly well maintained. In the present work care was taken to inject celluloid mass (celluloid and camphor dissolved in acetone) of equal strength (with contrast colors) into the two coronary arteries simultaneously and at the same pressure. At the same time, a thicker celluloid mass was injected into the cardiac cavities in order to make a cast of the interior of the heart. When the mass hardened, the muscle tissue was removed by corrosion in hydrochloric acid and subsequent washing in water.

For the demonstration of the blood supply of the interventricular septum, as shown in figure 1, only slight variation in the technic is necessary. A heart in which the foramen ovale is closed must be selected. Either side of the septum may be demonstrated if water is

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* From the Section on Pathologic Anatomy, the Mayo Clinic.

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, June, 1929.

1. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart: A Modification of the Celluloid and Corrosion Technic, *Arch. Int. Med.* **42**:846 (Dec.) 1928.

injected into that side of the heart, and the celluloid mass, in the usual manner, into the opposite auricle and ventricle. A cast is thus made of only one side of the heart, whereas the opposite side is distended at the same pressure to prevent distortion. The remainder of the technic is the same as that employed in making casts of the entire heart.

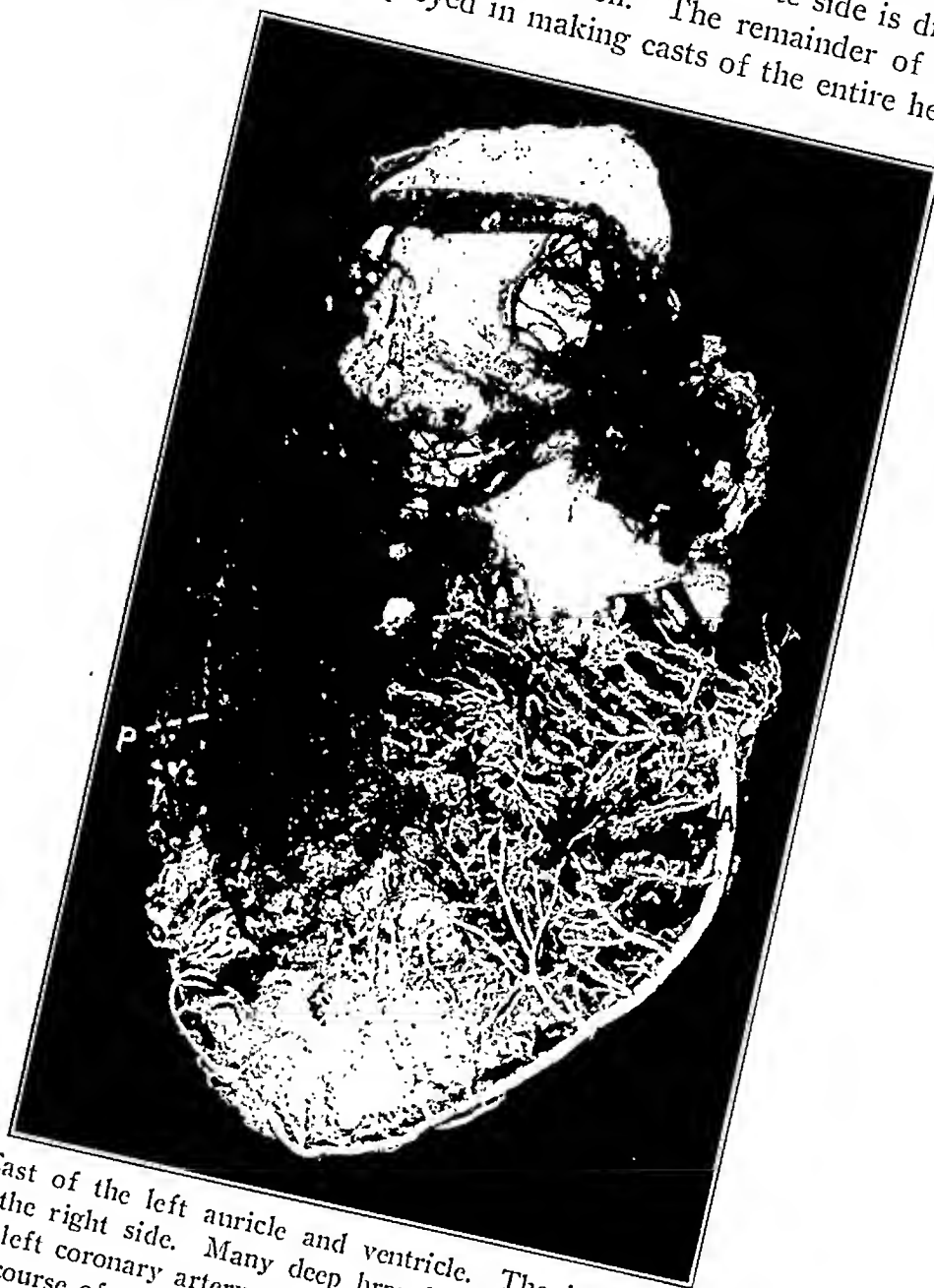


Fig. 1.—Cast of the left auricle and ventricle. The interventricular septum is seen from the right side. Many deep branches leave the anterior descending branch of the left coronary artery, at right angles, to supply the interventricular septum. The course of the anterior descending artery around the apex is shown, as well as the portion of the interventricular septum supplied by each coronary artery. *A* indicates the anterior descending artery (left coronary artery); *P*, the posterior descending artery (right coronary artery).

In the celluloid casts of the heart, since the myocardial tissue has been removed entirely, the deeper blood vessels are clearly seen even in the thicker left ventricle. The celluloid cast of the interior of the

heart shows the size, shape and contour of the chambers, forms a support for the blood vessels and depicts relationships even after all the tissues of the living heart have been corroded away. Celluloid injected into the arteries penetrates to the capillaries, but not through them; for this reason, the resulting cast accurately portrays the arterial tree uncomplicated by venous branches. Smaller vessels may be removed for microscopic study. All the structures are shown in three dimensions; hence, there is not the confusion in their interpretation that often occurs in the case of roentgenograms or even stereo-roentgenograms.

THE RELATIVE VASCULARITY OF THE TWO VENTRICLES

Gross² is the only one who has given any detailed account of the changes occurring in the relative vascularity of the right and left ventricles from birth, throughout life, to old age. A few men, such as Bizot,³ Valentin⁴ and Müller, have measured the relative thickness, weight or circumference of the two ventricles. Bizot's determinations (1837) are far from accurate. His measurements showed the left ventricle to be from 2.6 to 4.8 times as thick as the right, but did not show any variation that might suggest a difference in the relative thickness of the two ventricles at various ages. His only comparison of the circulation of the two ventricles was the observation that as a general rule the orifice of the left coronary artery was larger than that of the right, early as well as later in life. Valentin compared the thickness, weight and volume of the walls of the two ventricles. Regardless of the sex of the animal studied, he found that the ratio of the right ventricle to the left was always close to 1:2, no matter what measurements were compared.

According to Tandler,⁵ Beneke (1879) measured volumetrically the relative mass of the right and left ventricles. Beneke found the relationship of the mass (by volume) of the right ventricle to that of the left, in man, to be 1:2.26 between the ages of 17 and 25 years and 1:2.02 between the ages of 27 and 73 years. His figures indicate that there is no increase in the preponderance of muscle mass of the left ventricle, as compared with the right, after the period of 17 to 25 years of age. In fact, his data suggest decrease in the predominance of the left ventricle for the period between 27 and 73 years.

2. Gross, Louis: *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B. Hoeber, 1921.

3. Bizot, J.: *Recherches sur le couer et le Système Artériel chez l'Homme*, Mém. Soc. méd. d'obst. **1**:262, 1837.

4. Valentin, G.: *Ueber die Gegenseitigen Massenverhältnisse der Rechten und der Linken Kammer des Herzens*, Ztschr. f. rat. Med. **3**:317, 1844.

5. Tandler, Julius: *Anatomie des Herzens*, in von Bardeleben, Karl: *Handbuch der Anatomie des Menschen*, Jena, Gustav Fischer, ed. 3, pt. 1, 1913.

Müller's work (1883) on the relative weights of the right and left ventricles has been reviewed by Tandler. A portion of one of Müller's tables is given in the accompanying table, the second and third columns of which give Müller's figures for the average weights of the right and left ventricles at various ages. In the column at the extreme right, the ratio of the weight of the left ventricle to that of the right is shown. Although there is considerable variation, the predominance of the weight of the left ventricle, as compared with the right, increases from a ratio of 1.2:1 at 1 week of age up to 2:1 at 7 to 12 months of age. From the age of 12 months on there is considerable variation, but as a whole the ratio between the weights of the two ventricles remains

TABLE 1.—*Weight of the Right and Left Ventricles at Various Ages According to Müller and as Presented by Tandler**

Age	Right Ventricle (Including Septal Wall), Gm.	Left Ventricle (Including Septal Wall), Gm.	Ratio of Weight of Left Ventricle to That of Right Ventricle†
1 week.....	6.14	7.45	1.213
2 weeks.....	5.34	7.65	1.433
3 weeks.....	5.39	7.93	1.471
4 weeks.....	5.41	8.83	1.632
2 months.....	4.28	7.28	1.701
3 months.....	5.47	9.98	1.825
4 to 6 months.....	6.55	12.35	1.886
7 to 12 months.....	8.04	16.31	2.029
2 years.....	12.42	22.00	1.771
3 years.....	14.98	32.15	2.146
4 to 5 years.....	16.21	34.20	2.106
6 to 10 years.....	23.01	50.97	2.038
11 to 15 years.....	34.00	67.10	1.974
16 to 20 years.....	63.40	117.10	1.934
21 to 30 years.....	70.80	125.10	1.767
31 to 40 years.....	71.00	135.60	1.910
41 to 50 years.....	72.80	143.90	1.977
51 to 60 years.....	75.30	151.60	2.013
61 to 70 years.....	77.70	155.70	2.004
71 to 80 years.....	73.20	142.60	1.948
81 to 90 years.....	61.60	144.40	2.344

* This table represents the average weights of hearts of male human beings. The ratio between the weights of the two ventricles was essentially the same in females.

† I have calculated the relation of the weight of the left ventricle to that of the right from the results obtained by Müller and shown in the two preceding columns.

practically the same. Müller's results were interpreted by Gross as indicative of a constantly increasing preponderance of the weight of the left ventricle, as compared with the right, as age increased. The ratio of the weight of the left ventricle to that of the right, as calculated from Müller's data and recorded in the accompanying table, shows, however, that there is no consistent increase in the predominance of the left ventricle after the 7 to 12 month period of life has been reached.

Gross found that the right and left ventricles received about an equal blood supply at birth, and he believed that this ratio remained about the same until the second decade of life, when the left ventricle became a little more vascular than the right. In the third decade of life, Gross found the left ventricle to be definitely more vascular than the right, and he believed that there was an increasing pre-

dominance of the vascularity of the left ventricle as compared with the right throughout the succeeding decades of life. He explained that this was due, not so much to a definite loss in blood vessels on the right side, as to a relative loss as compared with the ever increasing vascularity of the left ventricle. In other words, he believed that the right ventricle lagged behind the left consistently and increasingly throughout life, as far as vascularity was concerned. Gross was inclined to believe that this loss of blood vessels, as compared with the left ventricle, produced an increasing decline and failure of the right side of the heart, and that this accounted for the frequency of deaths from pneumonia in elderly persons. He suggested that "a man is as old as his right coronary artery."

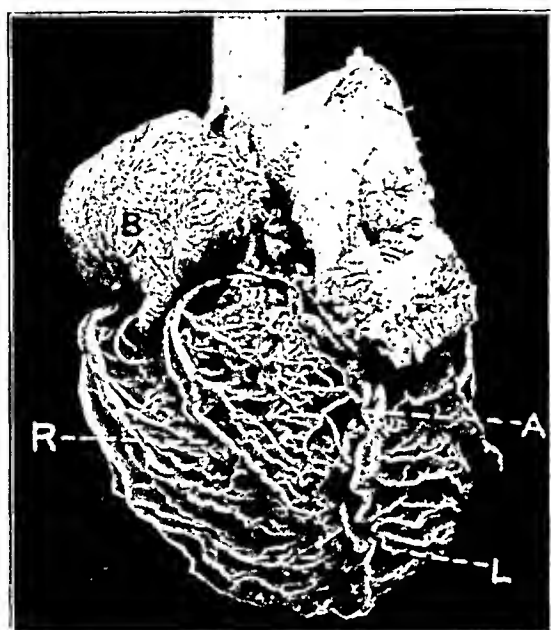


Fig. 2.—Anterior view of celluloid cast of heart of fetus at full term, showing equal vascularity of right and left ventricles. *R* indicates the right ventricle; *L*, the left ventricle; *A*, the anterior descending artery (left coronary artery); *B*, the right coronary artery.

Campbell⁶ (1928), using stereoscopic roentgen technic, asserted that he verified the work of Gross concerning the comparative vascularity of the ventricles. He stated: "The alteration in the relative vascularity of the ventricles which comes with advancing age, and results in a decrease of the blood supply to the right heart through an increase in the development of anastomotic branches was also verified."

In the work to be reported in this paper, a comparison was made of the blood supply of the two ventricles. The hearts were prepared

6. Campbell, J. S.: Stereoscopic Radiography of the Coronary Circulation, *Lancet* 2:168, 1928.

by the celluloid-corrosion method. The auricular circulation was excluded from this study because of its great variability and because it does not present a definite relationship to the ventricular circulation. The blood supply of the interventricular septum also has been excluded from the present study because of the difficulty of deciding what portion of the septum belongs to each ventricle.

Some time ago, my attention was called to the fact⁷ that in a cast of the heart and injected coronary vessels of a child who died at 13½ months of age, the left ventricle was much more vascular than

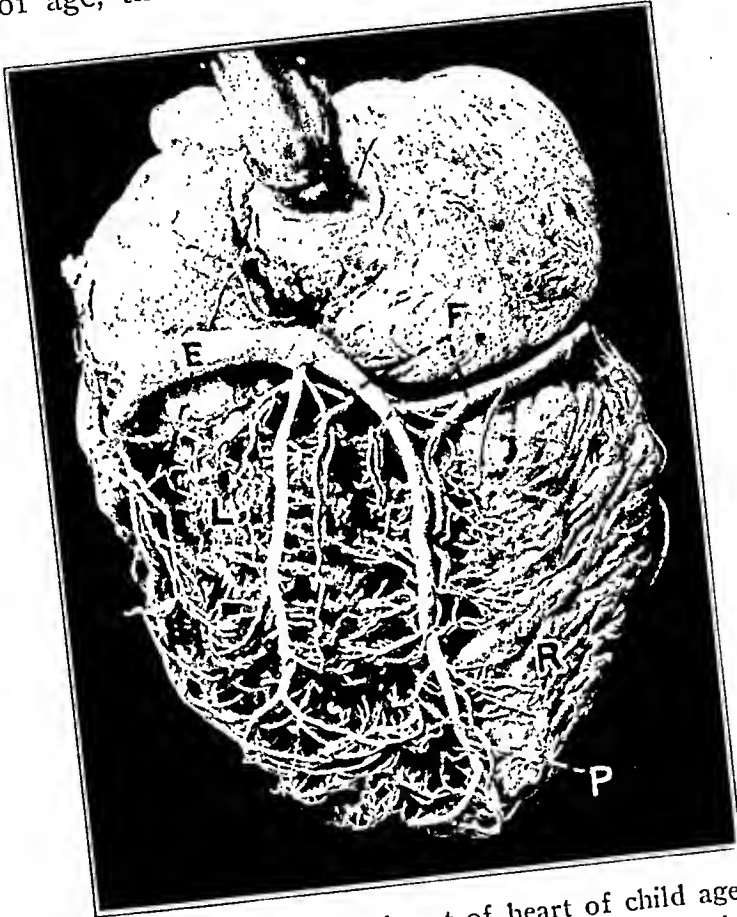


Fig. 3.—Posterior view of celluloid cast of heart of child aged 2 years, showing moderate vascular preponderance of the left ventricle. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

the corresponding right ventricle. This is contrary to the data of Gross. An anterior view (fig. 4) of this heart accompanied a previous paper.¹ As it is possible, however, that the two coronary arteries were not injected under exactly the same standard conditions in this preparation, care has been taken since to inject the two coronary arteries under the same standard conditions, and a number of hearts of chil-

7. Barnes, A. R.: Personal communication to the author.

dren of various ages have been studied in order to determine at what age the left ventricle becomes more vascular than the right. In order to compare the blood supply of the two ventricles, illustrations of celluloid casts are shown in figures 2 to 8. The blood vessels of a ventricle are fairly equally distributed, and the only reason for showing the posterior surface in most of the cases is that it presents a broad, flat surface which will show in a single photograph an equal portion of the two ventricles.

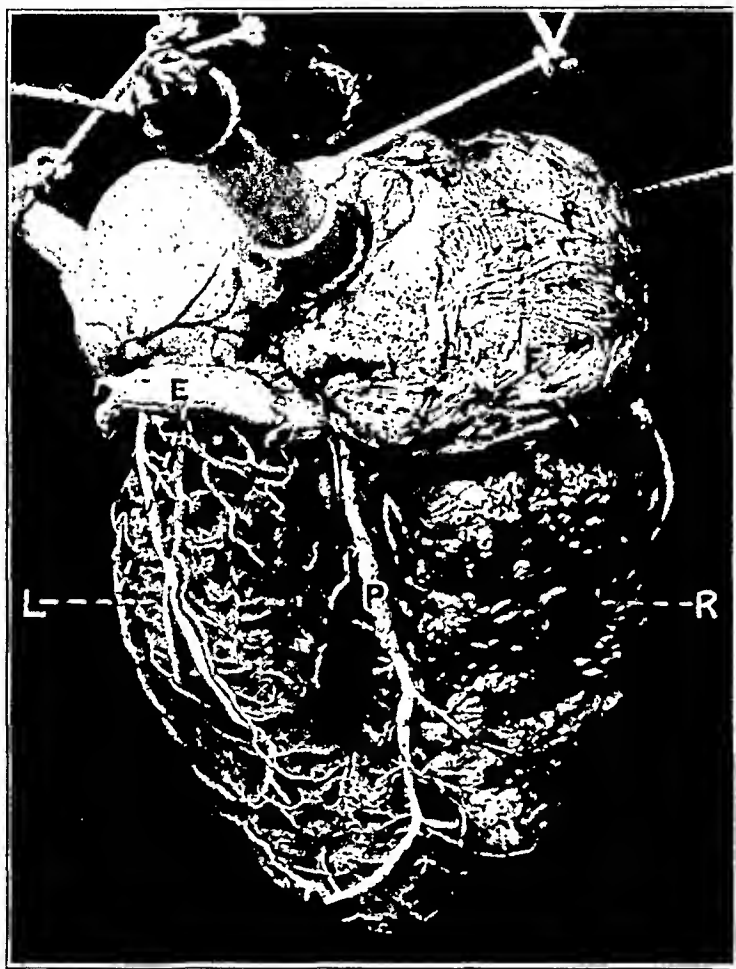


Fig. 4.—Posterior view of celluloid cast of heart from a child aged 6 years. The vascularity of the left ventricle predominates markedly over that of the right. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

STUDY OF HEARTS BY THE METHOD OF CORROSION

In the cast of the heart of a fetus of 6 months, the right and the left ventricles possess an approximately equal vascularity. In figure 2, an anterior view of the cast of the heart of a fetus at full term reveals equal vascularity of the two ventricles. At 2 years of age (fig. 3), the left ventricle is definitely more vascular than the right. This is not

so apparent in the base of the left ventricle, near the obtuse margin, for some of the branches of the left circumflex artery have been broken off. Elsewhere, however, the left ventricle has a more profuse blood supply than the right. In the fourth year of life, the left ventricle possesses rather marked vascular preponderance. At 6 years (fig. 4) the vascularity of the left ventricle has become still more marked than that of the right. This predominance is evident in spite of the fact that in the heart which was selected for study, a number of large

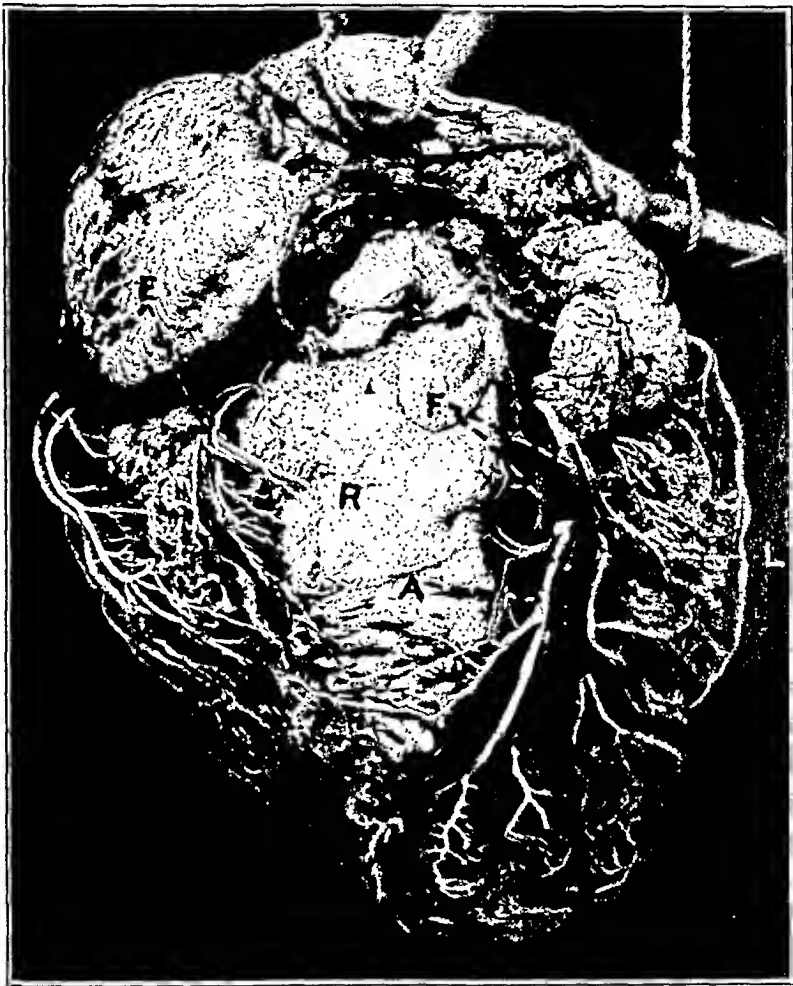


Fig. 5.—Anterior view of celluloid cast of heart of child, aged 10 years. The left ventricle is markedly more vascular than the right on the anterior as well as on the posterior surface of the heart. *R* indicates the right ventricle; *L*, the left ventricle; *A*, the anterior interventricular vein; *E*, the right coronary artery; *F*, the left coronary artery.

branches of the right coronary artery coursed transversely across the posterior surface of the right ventricle to supply the posterior portion of the interventricular septum. Usually these vessels arise from the deep surface of the posterior descending artery, as it follows down the posterior interventricular sulcus, and consequently, they are hidden from view and do not show on either ventricle. In the heart of the

child, aged 7 years, the left ventricle had a greater blood supply than the right, but the difference was not as marked as it was in the preceding cast.

In a previous paper¹ a posterior view (fig. 2) was presented of the cast of the heart of a child, aged 10 years. The vascularity of the left ventricle is extremely well developed and shows a marked predominance over the blood supply of the opposite ventricle. In fact,

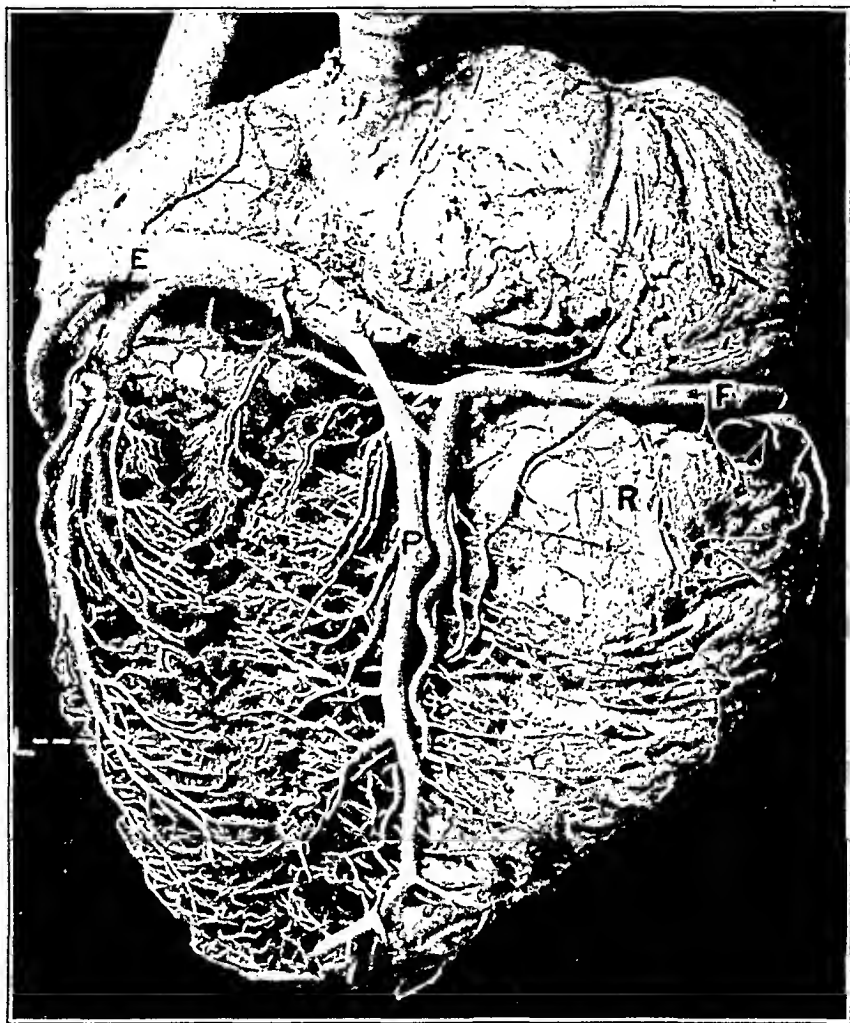


Fig. 6.—Posterior view of celluloid cast of heart from a child, aged 14 years. The left ventricle is markedly more vascular than the right. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

at 10 years of age, the vascular preponderance of the left ventricle appears to be as well developed as Gross found it to be one or two decades later. In order to demonstrate that the preponderance in vascularity of the left ventricle is not confined to the posterior surface of the heart, an anterior view of the same cast is shown in figure 5.

In the heart of the subject of 14 years of age (fig. 6), the vascular preponderance of the left ventricle is just as marked as it was at 10 years of age. The last two figures also show that the venous as well as the arterial circulation of the left ventricle predominates over that of the opposite ventricle.

As this study was begun to determine the age at which the left ventricle became better supplied with blood than the right, a special

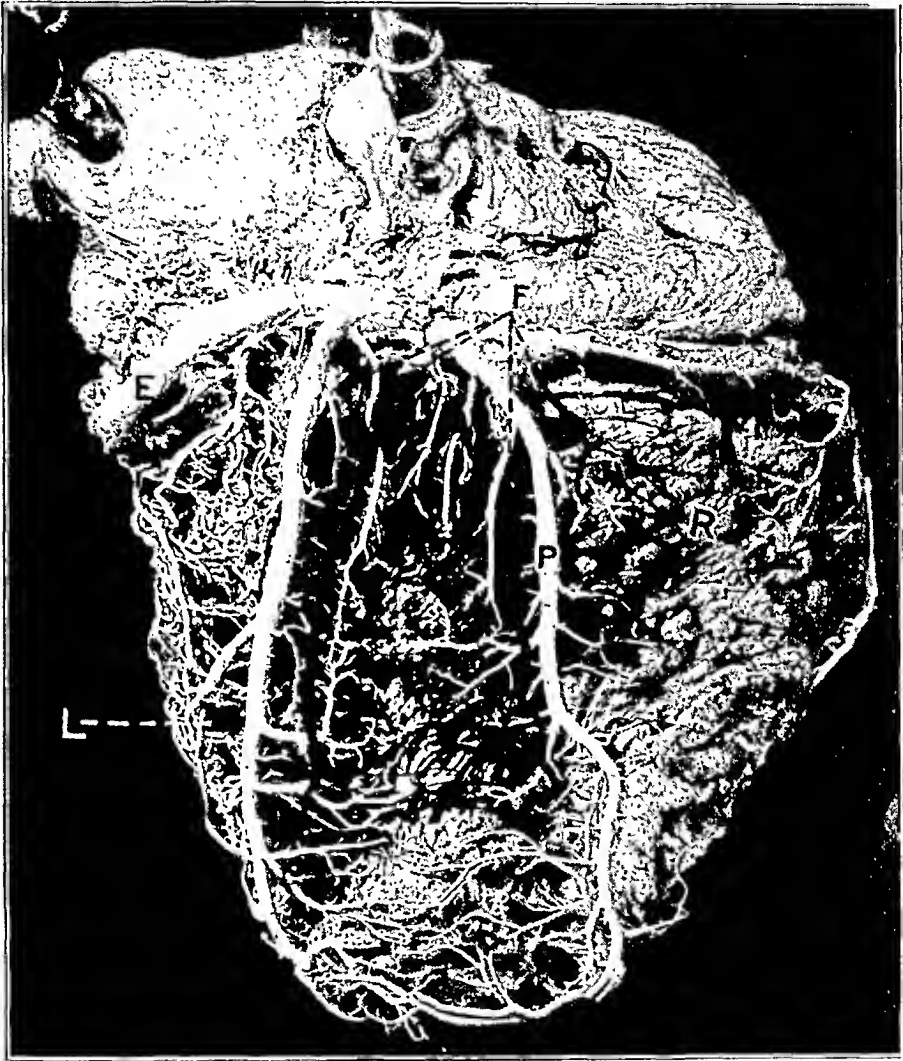


Fig. 7.—Posterior view of celluloid cast of heart from a woman, aged 28. The vascular preponderance of the left ventricle is evident. *R* indicates the right ventricle; *L*, the left ventricle; *P*, the posterior interventricular vein; *E*, the left coronary artery; *F*, the right coronary artery.

effort was made to secure a series of hearts of children. Since it is evident enough that the left ventricle is the more vascular in adult life, illustrations of only one cast of an adult heart are presented. This is from a patient who died at the age of 28 years (fig. 7). The left ventricle is definitely more vascular than the right.

All of the casts so far studied were made from normal hearts. In the cast illustrated in figure 8 the right ventricle is seen to be much

more vascular than that observed in the normal hearts of adults. This patient had a hypertrophied right ventricle and a corresponding increase in the blood supply of this portion of the heart.

COMMENT

The illustrations demonstrate that during the latter part of fetal life, and at birth, the right and the left ventricles are about equally vascular.



Fig. 8.—Celluloid cast of heart from a man, aged 71. There is increased vascularity of the hypertrophied right ventricle. *R* indicates the anterior surface of right ventricle; *E*, the branch of right coronary artery; *F*, the anterior descending branch of left coronary artery.

In fact, the blood supply of the two ventricles is so nearly equal that, unless one is familiar with the normal course of the vessels, one is likely to be at a loss to determine which is the right coronary artery and which the left.

It has been observed, also, that the left ventricle becomes more vascular than the right much earlier than the work of Gross would indicate.

Whereas he did not describe any difference in the vascularity of the two ventricles previous to the second decade of life, and did not find a marked difference in their relative vascularities until the third decade, the casts observed in this study indicate that the vascular preponderance of the left ventricle is well in evidence at the end of the second year of life, that by the sixth year it has become marked and that by the tenth year there is an enormous preponderance of blood vessels in the left ventricle. That this preponderance persists throughout life in normal hearts is indicated by the casts of adult hearts. The casts, therefore, demonstrate a preponderance that increases up to the tenth year of life, but which from that time on does not appear to increase with age but to continue at about the same ratio.

It has been shown also that there is an increasing venous preponderance in the left ventricle corresponding rather closely with that of the arteries.

The work of Müller (table) shows that during the first week of life the weight of the left ventricle is not much in excess of that of the right. If the weights of the two ventricles are studied with respect to the changes that occur with increasing age, it is found that the difference between them increases gradually but regularly until the age of 7 to 12 months. After this, there is no consistent increase in the preponderance of the left ventricle over the right with respect to weight. If Müller's work may be accepted as fairly accurate, it is evident from a study of the right hand column of the tabulation that there is no increasing predominance in the weight of the left ventricle throughout life; instead, after the age of 7 to 12 months there remains an almost constant ratio between the weights of the two ventricles. Beneke's work also indicates that there is no increasing preponderance of the weight of the left ventricle over that of the right after the ages of 17 to 25 years. Consequently, I cannot agree with Gross that Müller's work is indicative of a constantly increasing preponderance in the weight of the left ventricle.

In the heart at birth there usually cannot be demonstrated any difference in the thickness of the two ventricles. I have shown that at this time the two ventricles are equally well supplied with blood. In all of the remaining normal hearts studied, that is, from the age of 2 years on, the left ventricle was definitely thicker than the right. In these hearts, there was found to be a left-sided vascular preponderance in every case, and at the tenth year it was concluded that the predominance of the blood vessels in the left ventricle was so marked that an increasing preponderance could not be demonstrated thereafter.

The observations indicate that the vascularity in some degree is in relation to the weight and thickness of the ventricle. If Müller's

results are accepted, it would seem that the muscle weight reaches its constant ventricular ratio at an earlier age than the blood supply. Additional proof that there is some relationship between the thickness and the weight of the ventricle, and the blood supply, is evidenced by the increased vascularity that appeared in an hypertrophied right ventricle (fig. 8). Comparison of the blood vessels in the right ventricle, in this case, with those of the normal hearts, seen in the previous figures, will show this marked increase in circulation.

SUMMARY AND CONCLUSIONS

1. A method of demonstrating the circulation of the interventricular and interauricular septums by a modification of the celluloid corrosion technic has been described.

2. At birth and during the latter part of fetal life, the right and left ventricles are about equal in vascularity.

3. By the end of the second year, the left ventricle has become definitely more vascular than the right. This preponderance increases until about the tenth year of life, after which no increase in the vascular preponderance of the left ventricle could be demonstrated.

4. There is a definite preponderance of the venous circulation in the left ventricle as compared with that of the right.

5. It is suggested that there is some relationship between the thickness of the ventricular wall and its blood supply in the absence of marked arteriosclerosis.

COMPLETE HEART BLOCK

ROENTGEN-KYMOGRAPHIC STUDY *

J. MARION READ, M.D.

SAN FRANCISCO

This report is based on a study of two cases of complete heart block of many years' duration. The patients were unaware of the cardiac abnormality and suffered no discomfort or limitation of activity therefrom. While such cases of compensated, complete, auriculoventricular dissociation are not so rare as to warrant the report of additional ones, there are some aspects of this type of case which are worthy of further study.

UNUSUAL FEATURES IN COMPLETE HEART BLOCK

Some of the unusual features encountered are: (1) absence of symptoms of inadequate circulation, including Stokes-Adams' attacks; (2) increased size of the heart; (3) high systolic and normal, or low, diastolic blood pressures, and (4) variations in the pulse force or volume.

Absence of Inadequate Circulation.—The clinical details of the two cases studied with the roentgen-kymograph have been reported elsewhere.¹ One case was that of a woman, aged 47, in whom complete heart block had existed, in all probability, since an attack of diphtheria in childhood. The other was that of a man, aged 77, in whom heart block was of indefinite duration, but probably of ten or more years, and most likely arteriosclerotic in origin. In each case the block was discovered incidentally, as neither patient suffered from any circulatory insufficiency. It is this adequate compensation for a serious cardiac lesion which lends such interest to these cases, which show, as a rule, no evidence of cardiac damage other than complete auriculoventricular dissociation.

Regarding the unusual features of the cases mentioned, it is well known that Stokes-Adams' attacks cease to occur when an idioventricular rhythm above from 20 to 25 has become established.

Size of the Heart.—The second feature, supernormal size of the heart, is a necessary consequence of the increased stroke volume. The cardiothoracic indices in my two cases and in a similar one reported by Smith² were above 0.5. This enlargement of the cardiac shadow results

* Submitted for publication, July 21, 1929.

* From the Stanford University Medical School, Division of Medicine.

1. Read, J. Marion: A Clinical Interpretation of Pulse Pressure, *Am. Heart J.* **2**:541 (June) 1927.

2. Smith, S. C.: High Grade Heart Block; the Influence of Posture, Respiration and Exercise, *J. A. M. A.* **76**:17 (Jan. 1) 1921.

probably from two factors. One is muscle hypertrophy, but the greater cause is larger blood volume within the heart's chambers. The high systolic pressure would indicate ventricular hypertrophy, and there is some evidence of auricular hypertrophy in the high P wave (fig. 1). I am aware of no postmortem studies in this type of case which would assist in determining the amount of muscle hypertrophy.

Blood Pressure.—The third feature, normal diastolic and wide pulse pressure, I have commented on previously.¹ Musser,³ in 1917, reported some observations on two cases of complete heart block in women, aged 60 and 65. They each had normal diastolic and high systolic pressures, although in one the systolic pressure fell 100 mm. during a brief return to normal rhythm. From a study of his two cases and a review of the literature on heart block from 1904 to 1916, Musser concluded "That this high pressure is dependent more on increased blood mass discharged by the left ventricle than on the associated cardiac hypertrophy and peripheral sclerosis."

Stroke Volume.—It seems but logical to assume that stroke volume will have to be doubled when the pulse rate is reduced to half the normal rate if an adequate minute volume is maintained, as it is in compensated cases like the two I have studied.

That this is actually the case was shown by Lundsgaard⁴ in 1916, and more recently (1927) by Liljestrand and Zander,⁵ who studied the blood flow in a young man, aged 20, with complete heart block since childhood, but who "is able to perform very heavy muscular work and practises athletics." Following extensive studies of this man, the Swedish investigators said, "There can thus be no doubt that in this subject the low pulse rate is completely compensated by the increased ventricular output per beat, resulting in a normal blood flow. In this case, however, this also holds true during muscular work."

In a personal communication, Dr. A. V. Bock of the Massachusetts General Hospital gave me the data on the blood flow in another such patient, but with a constant 3:1 block. The pertinent data are: A man (A. B. C.), aged 58, had a pulse rate of 26 per minute. The blood pressure was 215 systolic and 100 diastolic. The blood flow was 3.68 liters per minute, or an output of 141 cc. per systole, which is nearly

3. Musser, J. H.: Heart Block Associated with High Blood Pressure. *Arch. Int. Med.* **20**:127 (July) 1917.

4. Lundsgaard, C.: Untersuchungen über das Minuten-volumen des Herzens bei Menschen: III. Messungen an zwei Patienten mit totalen Herzblock. *Deutsches Arch. f. klin. Med.* **120**:46, 1916.

5. Liljestrand, G., and Zander, E.: Studies of the Work of the Heart During Rest and Muscular Activity in a Case of Uncomplicated Total Heart Block, *Acta med. Scandinav.* **66**:501, 1927.

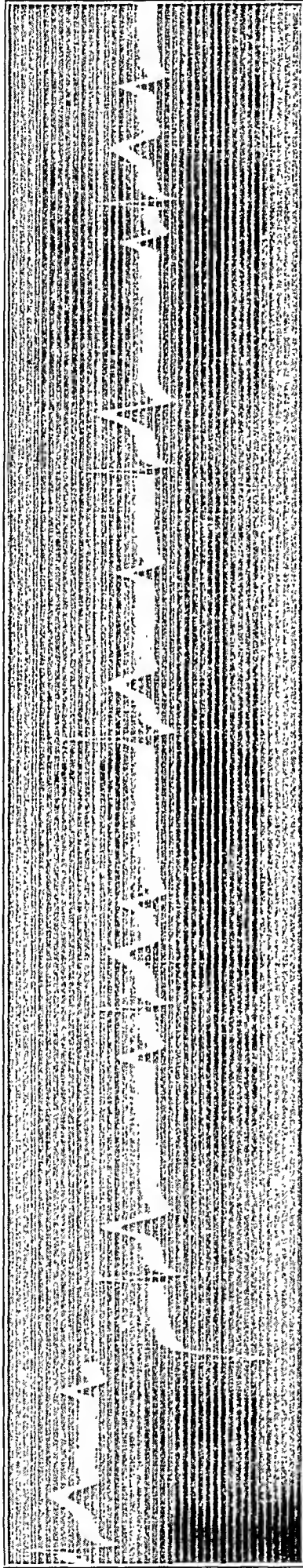


Fig. 1.—Second lead of the electrocardiogram in the case of a woman, aged 47. She had complete heart block since childhood. There were no manifestations of myocardial insufficiency. There is a high auricular wave in this and the other two leads.

double the average normal for a man weighing 146 pounds (66.2 Kg.). The interesting thing to note is the pulse pressure of 115 and the fact that there was compensation, for Dr. Bock wrote ". . . he assured me that he had come into the hospital only at Dr. White's request to have himself checked up, and he denied symptoms of any kind. He appeared in excellent health and was able to indulge in vigorous exercise without dyspnea." He had been under observation for five years.

THE ARTERIOGRAM

To the palpating finger the pulse in compensated, complete heart block feels very full and strong and, because of the long diastole, seems

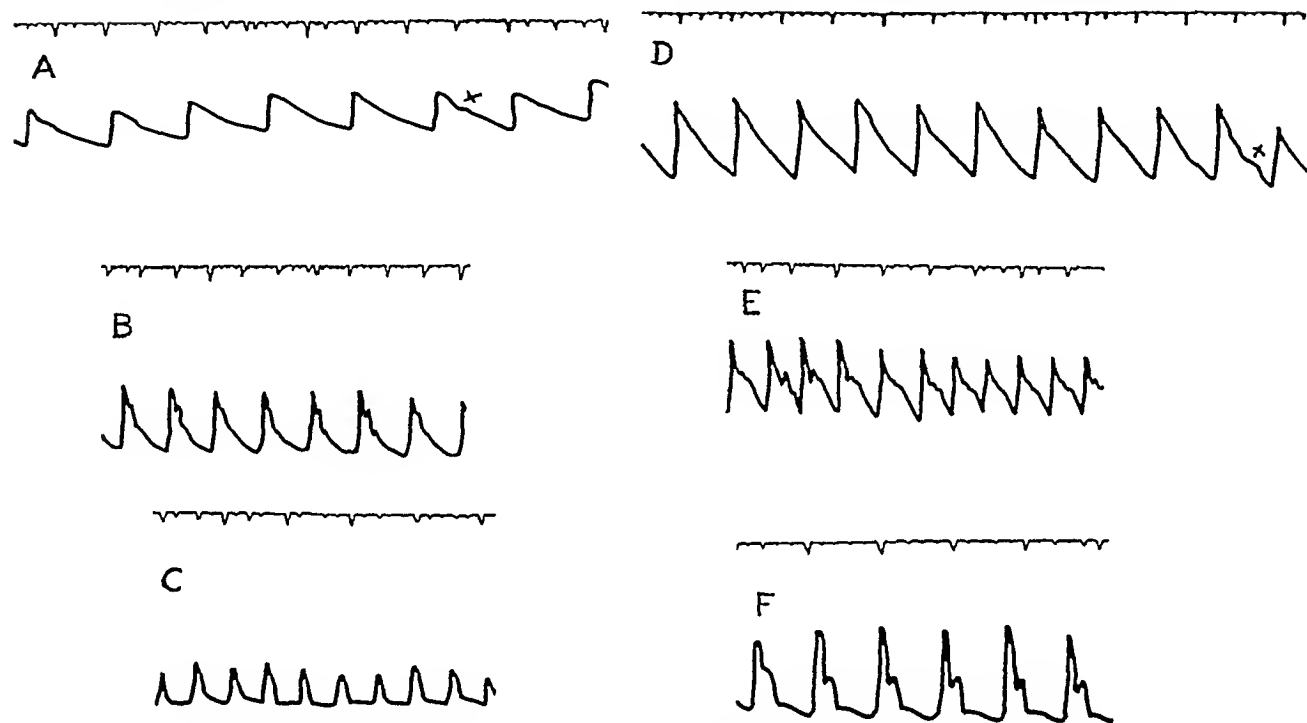


Fig. 2.—Arteriograms in complete heart block and aortic insufficiency with comparable blood pressures; these were retraced with india ink. In each of the heart block tracings is shown one of the notches which Mackenzie thinks are due to pressure on the base of the aorta from the contracting auricle. *A* (case 1), brachial arteriogram: blood pressure, 178 systolic and 82 diastolic; *B*, aortic insufficiency (syphilitic): blood pressure, 185 systolic and 42 diastolic; *C*, aortic insufficiency (syphilitic): blood pressure, 145 systolic and 45 diastolic; 178 systolic and 48 diastolic. *D* (case 2), brachial arteriogram: blood pressure, 170 systolic and 74 diastolic; *E*, aortic insufficiency (rheumatic): blood pressure, 116 systolic and 40 diastolic; *F*, aortic insufficiency: blood pressure, 135 systolic and 0 (?) diastolic.

to fall quickly. To ascertain the shape of the arterial wave and to compare it with arteriograms from cases of aortic insufficiency with approximately the same pulse pressure, I made several tracings, parts of which are shown in figure 2.

It is evident that the pulse wave in these cases more nearly resembles the normal, despite the deviation from normal pulse pressure, than it resembles the wave in aortic insufficiency with comparable blood pressures.

Because of the eccentricities of the polygraph, a comparison in height of the wave in patients with heart block and in normal subjects would be of little value. An interesting observation on this point was made by Musser³ when one of his patients was so obliging as to revert to normal rhythm while an arteriogram was being made. Musser said:

It is interesting to note the differences in size of the arteriogram waves where there is block and where the block has disappeared. The waves are almost twice as large when the rate is slow as compared with the heart beats when twice as rapid, demonstrating that where all other factors are equal, the adjustment levers being unchanged, a high pressure presumably causes large graphic arterial waves.

While it is inferred from the wide pulse pressure and height of the arterial wave that the stroke volume in compensated heart block is greatly increased, and this inference is borne out by experimental studies, there remains clinical confirmation by study of the heart itself.

THE ROENTGEN-KYMOGRAM

With a view to ascertaining several points which had arisen in a study of these cases of compensated, complete heart block, I undertook some investigations of the movement of the border of the heart. As roentgenograms of the heart in systole and diastole did not seem adequate or feasible, I resorted to the roentgen-kymograph as best suited to the purpose. This apparatus was first described in 1912 by Gott and Rosenthal,⁶ and has since been used by Becker,⁷ Crane⁸ and Cohn and Stewart⁹ in studying movements of the border of the heart.

Under the fluoroscopic screen the point of maximum ventricular movement was noted and its projection on the wall of the chest marked. The slit in the lead sheet was placed over this point and the roentgen-kymogram taken. It will be observed from figure 3 that in case 2 there is a marked difference between diastole and systole as denoted by the height and depth, respectively, of the waves. This is brought out by

6. Gott, T., and Rosenthal, J.: Ueber ein Verfahren zur Darstellung der Herz-bewegungen mittelst Röntgenstrahlen (Roentgenkymographie), München. med. Wchnschr. **59**:2033, 1912.

7. Becker, T.: Die Analyse des Elektrokardogrammes mittels der Röntgenkymographie, Deutsches Arch. f. klin. Med. **113**:216, 1914.

8. Crane, A. W.: Roentgenology of the Heart, Am. J. Roentgenol. **3**:513, 1916.

9. Cohn, G. E., and Stewart, H., Jr.: Evidence That Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation **1**:97, 1924.

comparison with a similar tracing from a normal male weighing 25 pounds (11.3 Kg.) more than the patient in case 2. Both roentgen-kymograms were taken under the same conditions, with the patients in a supine position, breath held, and at the same distance from target, etc. The tracings should be comparable, though I am aware of the criticism

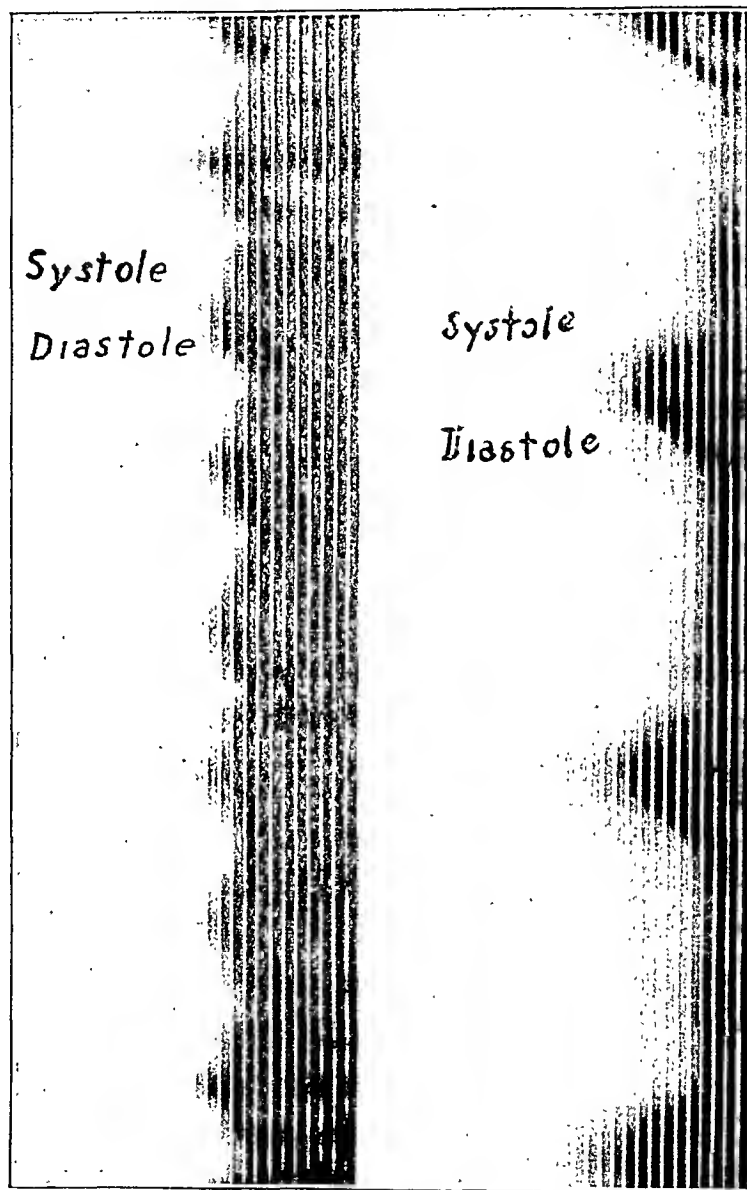


Fig. 3.—Roentgen-kymogram showing the curve produced by the point of maximum movement on the left ventricular border in a normal person and in a person with heart block, complete. The film moved past a 1 mm. slit in a lead shield, the slit being placed over the point of maximum movement as determined by fluoroscopic examination. The subject was prone; the speed of the film was about 4 cm. per second. Aside from the difference in heart rate, the chief point brought out by this comparison is the much greater amplitude of motion of the left ventricle in the case of heart block.

of this method of study by Stenström and Westermarck.¹⁰ They stated that the curves produced represent not only contraction of the border but traction and pushing from other parts of the heart. It seems most probable, however, that the marked differences in amplitude of ventricular movement seen in figure 3 are due to differences in systolic output and not to differences in traction or pushing since these should be approximately the same in each case.

It is recognized that movement at one point cannot be accepted as proof that the whole ventricle had as great an amplitude of motion, but great amplitude was confirmed by fluoroscopic examination and roentgen-kymograms taken at several points on the heart's border.

It becomes evident from the roentgen-kymogram that a patient with complete heart block, wide pulse pressure, high wave in the arteriogram and Corrigan-like pulse also has great amplitude of ventricular movement. By correlating these observations with the fact that such a patient is completely compensated with a pulse rate approximately one-half the normal, the clinician seems justified in attributing these phenomena to increased diastolic filling and the ejection of a supernormal volume of blood at ventricular systole.

EFFECT OF AURICULAR SYSTOLE

The obvious efficiency of the ventricle in compensated, complete heart block leads one to wonder about the effectiveness of auricular contractions in these patients. What is the relative importance of auricular contraction and venous pressure in filling the ventricle so completely?

The question has long been debated as to whether or not, even under normal conditions, auricular systole plays much part in filling the ventricle. Feil and Katz¹¹ studied the problem in a patient with alternating periods of auricular fibrillation and normal rhythm, using the duration of systolic ejection and total systole as criteria and concluded that their observations "give probable if indirect evidence of the dynamic importance of auricular systole in the normal heart beat of man."

I am not aware of any studies of the effectiveness of auricular systole on ventricular filling in complete heart block. But in seeking an explanation for the variations in the height of systolic pressure and variations in first sound intensity at the cardiac apex, I have come to the belief that these phenomena are due to different diastolic volumes expelled at systole. Variations in force of beat are present in auricular fibrillation and

10. Stenström, N. G., and Westermarck, N.: A Study of the Activity of the Human Heart Simultaneously Recorded by X-Rays and Electrocardiogram, *Acta radiol.* 5:408, 1926.

11. Feil, H. S., and Katz, L. N.: Evidence of the Dynamic Importance of Auricular Systole in Man, *Proc. Soc. Exper. Biol. & Med.* 20:323, 1922-1923.

in the first normal beat following a ventricular premature systole, long diastolic periods preceding the large beat in each case. But in complete block in which the ventricular rhythm is regular, variations in the force of beat seem logically best explained by variations in the number of auricular contractions occurring during ventricular diastole, venous pressure being constant. I realize, however, that there is little support for this conception since the general belief, based on the work of Henderson, Straube and others, is that the auricular contraction plays little or no part in filling the ventricle.

But Gesell,¹² working with the heart-lung preparation, showed that "under the conditions of these experiments auricular systole increased ventricular output 50 per cent over that maintained by venous pressure alone." His results seem unequivocal and, since the problem is chiefly one of hydrodynamics, it does not seem unreasonable to assume that in human beings with complete heart block auricular systole plays a part in filling the ventricle. I am inclined to this view because it is the only explanation I can give of two phenomena observed in the clinical study of the two cases of heart block which inspired this report.

Variable Systolic Force.—The first of these phenomena is the variation in systolic pressure, already mentioned, which at times seemed to me like an alternation. That a variation in the height of the systolic pressure occurs with successive contractions I am certain from repeated sphygmomanometric studies, nor does this seem to be due to respiratory phases as it occurs in successive beats and not in cycles. Whether or not these variations result from variable volumes of blood ejected at successive beats, I cannot be sure. The roentgen-kymogram shows a variability in the size of successive systoles. Also the arteriograms show this, but because of the mechanical defects inherent in this method, I hesitate to stress this evidence strongly.

It is more difficult to show that variable volumes are present in the ventricle because different numbers of auricular contractions occurring during ventricular diastole have forced variable volumes into the ventricle. Such an explanation does not seem unreasonable from a study of the electrocardiogram in figure 1. The roentgen-kymograms (figs. 4 and 5) seem to show that the shape of the ventricular curve is influenced by the number and time of the auricular systoles occurring during ventricular diastole.

The other phenomenon was pointed out to me by the roentgenologist who made a fluoroscopic examination of one of these patients. During this examination a curious movement of the left ventricle was seen.

12. Gesell, R. A.: *Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation, and Stimulation of the Vagus Nerve*, Am. J. Physiol. **40**:367, 1916.

READ—HEART BLOCK

namely, relaxation seeming to occur in two stages; during the long diastole the ventricle would expand in the normal manner, but in a moment there would be a second enlargement of the ventricular shadow. This phenomenon was produced, I believe, by the normal early diastolic filling from venous pressure, possibly augmented by an auricular contraction, and, later in diastole another auricular contraction added to the volume of blood already in the ventricle and produced the second distention of the ventricle observed under the fluoroscope.

This patient's electrocardiogram shows usually an auriculoventricular ratio of about 2:1, and during the greater number of ventricular diastolic periods two auricular systoles occur. In a continuous electro-

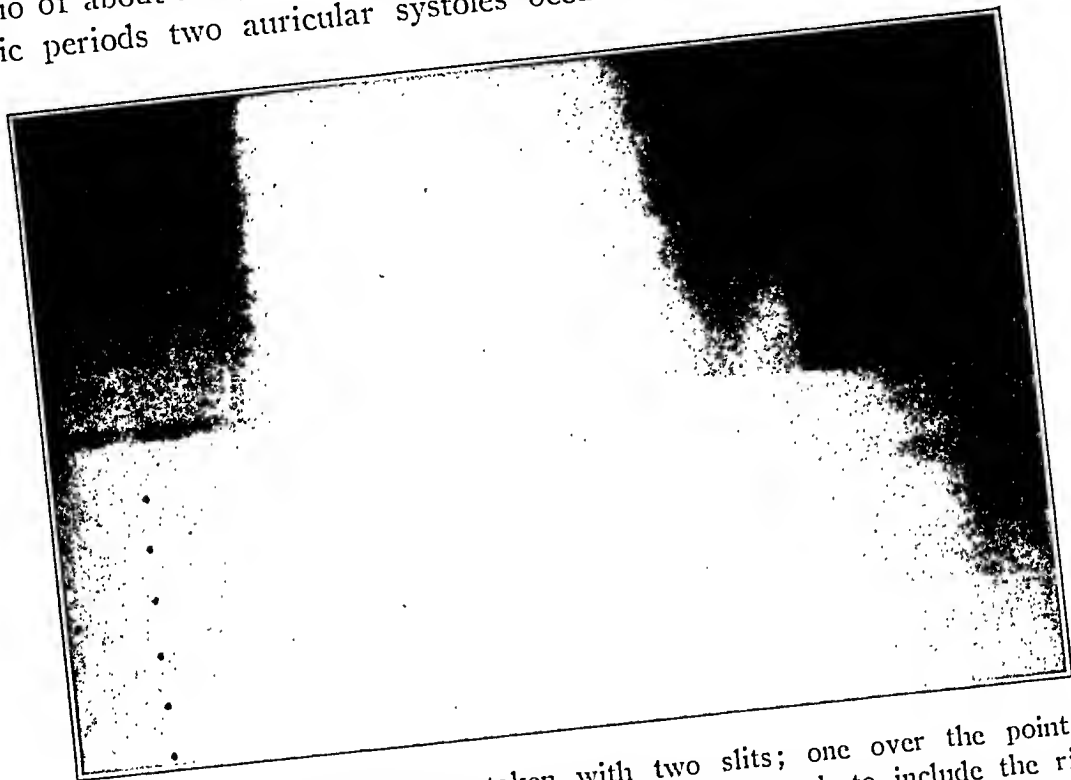


Fig. 4.—Roentgen-kymogram taken with two slits; one over the point of maximum movement of the left ventricle and long enough to include the right auricular border. The other slit, 4 cm. above the first, shows the movement of the aorta and vena cava. The film moved 1 cm. per second. The auricular systoles are marked by dots. Four ventricular and six auricular systoles are shown. The first, third and fifth auricular systoles occur close to the time of ventricular systole and produce larger waves in the vena cava. The shape of the ventricular systole not constant, the second one having a more acute corner (the first part of diastole) produced, it seems, by an auricular systole occurring early in diastole. A small tip on the third ventricular curve may be due to auricular systole late in ventricular diastole.

cardiographic tracing $9\frac{1}{2}$ feet long there were sixty-five heart cycles, and of this total two P waves fell in the diastolic period forty-two times. The roentgen-kymogram in this case shows that diastole is not a perfectly smooth curve (fig. 5) and also that there is a variation in the extent of diastolic filling amounting to 50 per cent in some instances.

There have been two other phenomena observed in cases of complete heart block and several theories offered in explanation thereof. One is variation in the first heart sound and the other is varying interauricular space.

Variable First Sound.—On listening to the first heart sound in patients with complete block I have observed a variability in its intensity and quality. This has also been noted by others and has been commented on by Carter and Howland¹³ as follows:

The first sound is usually not very loud. From time to time, however, there is a marked accentuation of this sound. . . . the very striking occasional accentuation of the first sound of the heart was a conspicuous feature and was interpreted as being due to the synchronous systole of auricle and ventricle, although auricular systole falling in the long diastolic pauses could not be made out.

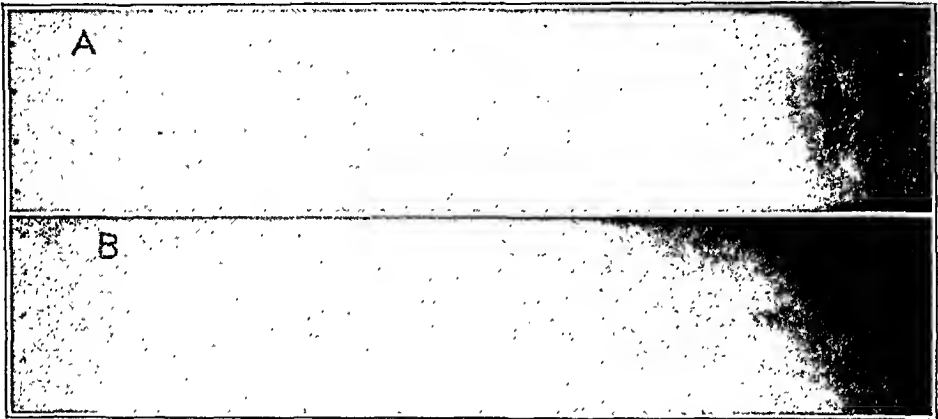


Fig. 5.—Roentgen-kymograms taken in the same manner as that shown in figure 4, but with one slit only, over the point of maximum movement on left ventricular border. Both show variability of the ventricular curve from cycle to cycle. *A* shows one complete ventricular cycle between the parts of two others. There are four auricular systoles shown, the third one coming too late in ventricular diastole to add anything to the intraventricular blood volume which apparently is much less than the volume at the preceding and succeeding systoles as indicated by the lesser ventricular distention of the intermediate cycle. *B* shows two complete ventricular cycles and five auricular systoles, the fourth one of which occurs late in diastole of the second ventricular cycle and appears to have produced a small "tip" on the ventricular curve just before systole.

An equally reasonable explanation of this occasionally accentuated first sound is that it results from ventricular contraction on an unusually large volume of blood. Simultaneous blood pressure readings might elucidate this point, as also might pulse tracings. But in respect to the

13. Carter, E. P., and Howland, J.: A Note Upon the Occurrence of Congenital Atrioventricular Dissociation: Report of a Case of Congenital Complete Heart Block, *Bull. Johns Hopkins Hosp.* 31:351 (Oct.) 1920.

latter, the mechanical factor introduces elements which render it almost impossible to place much reliance on small differences in the shape or size of arteriograms. At this point, however, I wish to remark that the shape of the arteriogram in complete heart block seems rather constant even with different machines in the hands of different investigators.¹⁴ These all show a small, if any, dicrotic notch and a gradual return to the base line (fig. 2).

Variable Interauricular Space.—When complete atrioventricular dissociation has become established, the upper chambers, while they beat at their own rhythm, are not uninfluenced by ventricular systole. Wilson and Robinson¹⁵ studied this phenomenon and summarized the literature. They observed that “the interauricular periods during which a ventricular systole occurred were shorter than those following the ventricular contraction.” This was especially noticeable when the auricular rate was slow, and has been explained by Erlanger and Blackman¹⁶ as due to “variations in vagal tone, vagus inhibition increasing with each arterial pulse and diminishing again between pulses.”

In addition to this explanation I wish to offer another reason for variable interauricular periods; namely, different intra-auricular pressures depending on the volume of blood (amount of resistance) in the ventricle. This assumes that the auricular muscle behaves like other muscle and contracts more strongly, having an automatic rhythm, more frequently, when it meets with an increasing intraventricular pressure on succeeding contractions. Erlanger and Blackman¹⁶ found that “the first auricular cycle following a ventricular contraction is long, but that the successive auricular cycles shorten until the ventricles again contract.”

This point is illustrated in figure 6, which reproduces an electrocardiogram taken in a case of incomplete and variable heart block. In lead 2 is shown a period of ventricular asystole lasting for more than four seconds during which six auricular systoles occur. The first two P waves are eighteen twenty-fifths of a second apart and the succeeding waves occur at shorter and shorter intervals until the last two are separated by an interval of only sixteen twenty-fifths of a second.

14. Mackenzie, J.: *Diseases of the Heart*, ed. 3, London, H. Frowde, 1921, p. 274. Hewlett, A. W.: *Pathological Physiology of Internal Diseases*, New York, D. Appleton & Company, 1923, p. 66.

15. Wilson, F. N., and Robinson, G. C.: Heart Block; I. Two Cases of Complete Heart Block Showing Unusual Features, *Arch. Int. Med.* **21**:166 (Jan.) 1918.

16. Erlanger, J., and Blackman, J. R.: Further Studies in the Physiology of Heart Block in Mammals: Chronic Auriculo-Ventricular Heart Block in the Dog, *Heart* **1**:177, 1909-1910.

It will be observed that when the ventricle does contract after the long asystole it empties itself with a contraction of ectopic origin. If one credits the auricle with an appreciable power of filling the ventricle it does not seem unreasonable to suppose that six fillings from the auricle produced sufficient distention of the ventricle to stimulate a contraction. In lead 3 (fig. 6) there are shorter periods of ventricular asystole in which three auricular contractions occur, and in each instance the ventricular contraction terminating the long pause is ectopic in origin.

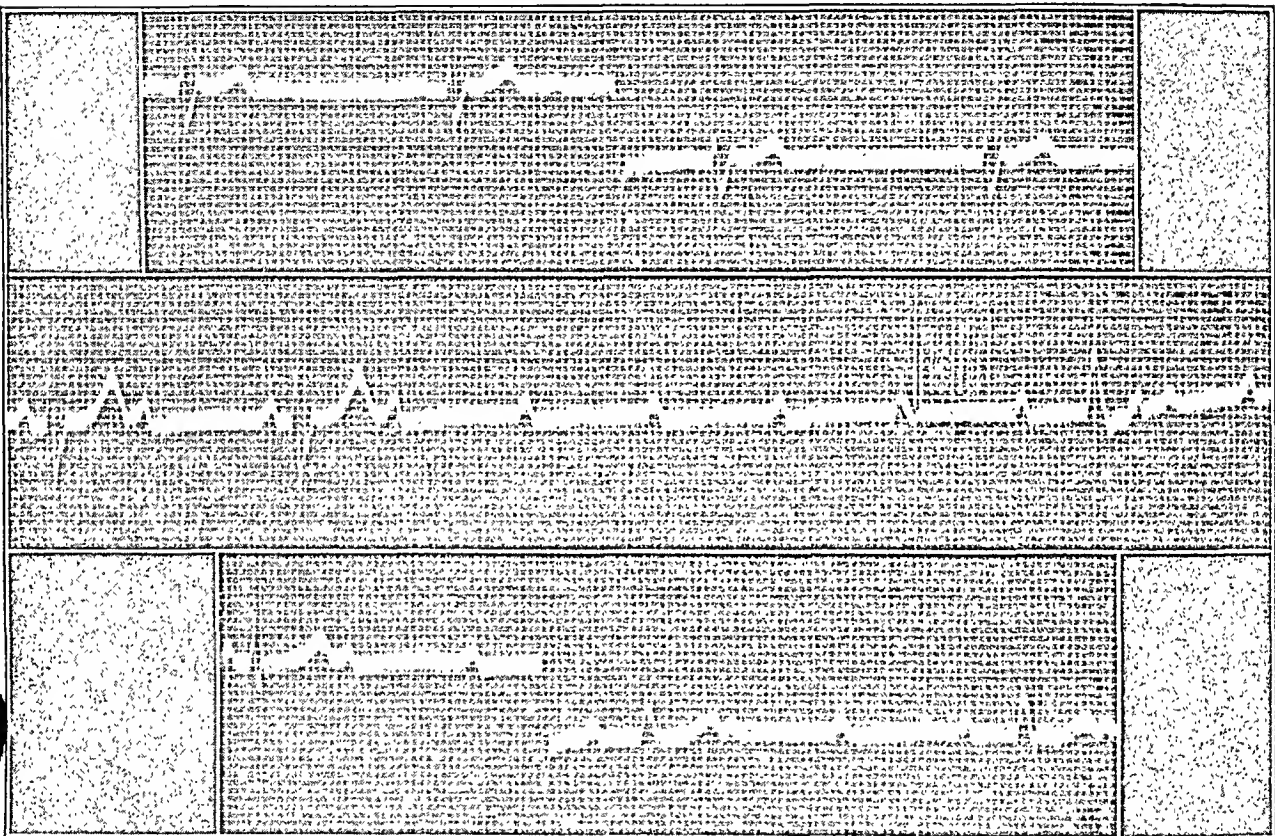


Fig. 6.—Incomplete heart block with variable ventricular response. In the second lead there is a period of ventricular asystole lasting for more than four seconds, during which the auricle contracts six times, the interauricular periods becoming progressively shorter. The long period of ventricular asystole is terminated by a contraction of ectopic origin as are similar but shorter periods in the third lead.

SUMMARY

Two patients with long-standing, complete heart block were studied with a view to obtaining further clinical evidence of the mechanism by which they maintained an adequate circulation with a pulse rate below 50. Increased size of the heart and wide pulse pressure with normal

diastolic blood pressure were noted, as well as wide amplitude of movement of the ventricular border.

Variability of stroke volume was surmised because of : (1) inequality of the first heart sound at successive systoles,¹⁷ (2) variable heights of systolic pressure and (3) the different shape of the roentgen-kymographic curves produced by ventricular systole. This variability seems to be due to the fact that different numbers of auricular systoles occur during ventricular diastole, and a more important rôle in filling the ventricle is attributed to auricular systole than it is customary to assign to it.

17. Since this paper was submitted for publication, a case similar to these two has been reported by Harris (*Heart* 14:289, 1929). From hospital notes made when his patient first came under observation in 1901, it is learned that "the first heart sound is not always the same, sometimes it is louder than otherwise. Sometimes it is very weak, sometimes quite sharp, varying about every four to six beats." Dr. Harris now records that "the first sound varies in intensity at the apex, as it was noted to vary 28 years ago." The blood pressure in his case was 202 systolic and 120 diastolic.

THE TREATMENT OF PNEUMONIA BY INHALATION OF CARBON DIOXIDE

I. THE RELIEF OF ATELECTASIS *

YANDELL HENDERSON, PH.D.

AND

HOWARD W. HAGGARD, M.D.

NEW HAVEN, CONN.

AND

POL N. CORYLLOS, M.D.

AND

GEORGE L. BIRNBAUM, M.D.

NEW YORK

WITH THE COLLABORATION OF ELLEN M. RADLOFF, B.S.

CAPE TOWN, SOUTH AFRICA

The problem of pneumonia is peculiar. The pathogenic organisms involved are as well known as those of typhoid or of diphtheria. Yet the mortality from such diseases as typhoid and diphtheria has been reduced far toward the vanishing point, while the mortality from pneumonia per hundred thousand of the population is almost the same as it was fifty years ago.

This lack of progress in the prevention and cure of pneumonia is the more noteworthy in view of the fact that the problem has been attacked as actively as that of other diseases by many able investigators using the methods of bacteriology, serology and preventive medicine. Thus the idea suggests itself that pneumonia may involve some factor that is not concerned in the other diseases and is not to be overcome by the methods effective against them. The factor peculiar to pneumonia may require treatment along a special line.

There is such a factor. It is one with which the internist is usually little concerned. For this reason it was long overlooked in pneumonia and has now only come to light through observations on the pneumonia following surgical operations. It is a factor with which surgeons are familiar; namely, occlusion of an infected organ and lack of drainage.

This new conception of pneumonia is that, as the infection takes place by way of the respiratory passages, it is of critical importance to keep

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* From the Laboratory of Applied Physiology, Sheffield Scientific School, Yale University, and the Department of Surgical Research, Cornell University Medical School.

these passages open and drained. The bronchoscope has even been used for this purpose. According as the airways are closed or open, the infection is influenced to become acute or is ameliorated. This influence is exactly the same as that of the drainage or occlusion of a localized infection in any other part of the body.

Nature has provided the lungs with several protective devices and reactions. The most obvious is the cough reflex by which irritating foreign bodies are removed. Less obvious, but more constantly acting, are the movements of respiration which are probably accompanied by peristaltic contractions and relaxations of the air tubes. The mucosa lining these tubes bears cilia which produce a continual flow of secretion from the depths of the lungs outward.

Occlusion of an air tube puts all of these mechanisms for the clearing of the lungs out of action. The air in the occluded portion of the lung is soon absorbed, and the alveoli are deflated and collapsed. They are then gradually filled by accumulation of secretion. The conditions resulting are in all respects favorable to the development of micro-organisms and, correspondingly, unfavorable both to the general defenses of the body and the special defenses of the lungs. It is a highly significant fact, as revealed by experiment, that in order to induce pneumonia in dogs it is not enough merely to introduce the pathogenic organisms into the lungs; it is essential also to narcotize the animals so deeply that the cough reflex is abolished and respiration is depressed. In general, depressed or shallow breathing tends to permit the development of pneumonia, and deep breathing with full ventilation of the lungs tends strongly to inhibit it.

ATELECTASIS AS A FACTOR IN PNEUMONIA

The critical importance of occlusion and collapse of the lung in the development of pneumonia might not have been discovered for a long time if investigation of another condition had not brought it to light. This was the occurrence of some degree of collapse of the lung in at least 10 per cent of all patients after surgical operations. The condition is seen particularly in patients who have undergone abdominal operations and whose breathing is thereafter impeded by the pain of the wound.

In tracing this matter still further it appears probable that the mechanism of collapse of the lung or, as it is better termed, atelectasis or apneumatosi (Coryllos), would not have been solved except for the fact that it was observed that this condition also results from the occlusion of a bronchus in diphtheria and from the plugging of a bronchus by a foreign body entering through the larynx and the trachea.

Thus, the evidence up to this point runs: Obstruction of a bronchus induces atelectasis. Atelectasis often follows surgical operations and is

the condition precedent to postoperative pneumonia. Atelectasis gives to pneumonia the character of an occluded and undrained infection. This is the conception which investigation led Coryllos and Birnbaum¹ to formulate. Pneumonia is, in fact, as they define it, a "pneumococcic atelectasis."

Meanwhile, along other lines, the investigations of Henderson and Haggard resulted in the discovery² that inhalation of carbon dioxide is under several different clinical conditions, a preventive of pneumonia. The explanation of this effect is now found in the fact that deep breathing induced by inhalation of carbon dioxide dilates the lungs and thus prevents or relieves atelectasis. The principal conditions in which atelectasis and pneumonia are associated and in which inhalation of carbon dioxide is indicated as a preventive are as follows:

ATELECTASIS AND PNEUMONIA IN THE NEW-BORN

Before birth the lungs are normally atelectatic. Although the first cry is the sign that the lungs have been at least partially distended, it is fairly common for parts of the lungs to remain undistended for a considerable time. Such a continuance of atelectasis is recognized as predisposing to pneumonia.³ To overcome a continuance or recurrence of the condition it is an ancient custom to make the child cry for fifteen minutes or more twice a day. The substitution of inhalation of 5 per cent carbon dioxide would be more in accord with the teachings of physiology. Such an inhalation has in fact been introduced by Henderson⁴ as the most effective means of overcoming asphyxia in the new-born and has been widely adopted. It is probable that the routine use of this inhalation on all infants, those that breathe spontaneously, but often incompletely, as well as those which do not breathe without some additional stimulus, would go far to eliminate the occurrence of pneumonia during the first few weeks of life.

1. Coryllos, Pol N., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung; Bronchoscopic Investigation, *Arch. Surg.* **18**:190 (Jan.) 1929; *Bull. New York Acad. Med.* **4**:384 (March) 1928.

2. Henderson, Y., and Haggard, H. W.: Hyperventilation of the Lungs as a Prophylactic Measure for Pneumonia, *J. A. M. A.* **92**:434 (Feb. 9) 1929. Henderson, Y.; Coryllos, P. N.; Haggard, H. W.; Birnbaum, G. L., and Radloff, E. M.: The Relief of Experimental Pneumonia, *Proc. Nat. Acad. Sc., Science* **69**:502 (May) 1929; The Production and Relief of Atelectasis of Pneumonia, *Am. J. Physiol.* **90**:317 (Oct.) 1929. Henderson, Y.; Coryllos, P. N.; Holmes, G. W., and Scott, W. J. M.: Symposium on Atelectasis and Pneumonia, *J. A. M. A.* **93**:96 (July 13) 1929.

3. Holt, L. E., and Howland, J.: *Diseases of Infancy and Childhood*, part 2, ed. 8, Chapters 1 and 2, New York, D. Appleton & Company, 1922.

4. Henderson, Y.: The Prevention and Treatment of Asphyxia in the New-Born, *J. A. M. A.* **90**:583 (Feb. 25) 1928.

POSTOPERATIVE PNEUMONIA

A death from pneumonia occurs now on the average, even in the best surgical practice, after each 240 major-operations.^{4a} Nonfatal pulmonary complications occur frequently. It was shown, however, in papers of the highest importance for the development of this subject, by Scott and Cutler⁵ in America and by Dzialoszinski with Meyer⁶ and by Fisher⁷ in Germany, that liability to postoperative atelectasis, massive, lobar or lobular, and to the pneumonia which frequently ensues, may be greatly reduced, indeed almost eliminated, by the routine administration of carbon dioxide at the termination of anesthesia and operation. That the benefit is due to the effects of carbon dioxide, rather than to the oxygen administered with it, is indicated by the fact that in German surgical practice the carbon dioxide is mixed merely with air without the addition of oxygen. The prophylactic effect of carbon dioxide in the prevention of postoperative pulmonary complications is clearly due to the full inflation of the lungs by the deep breathing induced by the inhalation.

It is probable that many previous observers have had premonitions on this matter; for Osler and McCrae⁸ said: "The diagnosis of massive collapse of the lung after operation or injury may be difficult, especially [its differentiation] from lobar pneumonia. . . . In treatment, change in position . . . and encouraging the patient to breathe deeply help in prevention." Meltzer⁹ had premonitions of this sort, but he was opposed to the conception, advocated in this country by Henderson,¹⁰ of the physiologic and therapeutic control of respiration by carbon dioxide.

4a. Smith, M. K., and Morton, P. C.: Postoperative Pneumonia, *Arch. Surg.* **18**:2167 (May) 1929.

5. Scott, W. J. M., and Cutler, E. C.: Postoperative Massive Atelectasis, *J. A. M. A.* **90**:1759 (June 2) 1928. Elwyn, H.: Postoperative Pneumonia, *J. A. M. A.* **8**:384 (Feb. 2) 1924. Sise, L. F.; Mason, R. L., and Bogan, I. K.: Prophylaxis of Postoperative Pneumonia: Preliminary Report of Some Experiments After Upper Abdominal Operations, *Anesth. & Analg.* **7**:187 (May-June) 1928.

6. Dzialoszynski, A.: Apparat zur Kohlensäureinhalation und bildliche Darstellung der Kohlensäureanwendung am Kranken, *Deutsche Ztschr. f. Chir.* **205**:22, 1927.

7. Fisher, E.: Prevention of Postoperative Lung Complications by Inhalation of Carbon Dioxide, *Zentralbl. f. Gynäk.* **52**:2010 (Aug. 11) 1928.

8. Osler: *Principles and Practice of Medicine*, revised by Thomas McCrae, ed. 10, New York, D. Appleton & Company, 1926, p. 659.

9. Meltzer, S. J.: Ueber eine Methode zur experimentellen Erzeugung von Pneumonie und ueber einige mit dieser Methode erzielte Ergebnisse, *Berl. klin. Wchnschr.*, July 20, 1914, p. 1351.

10. Henderson, Y.: Fatal Apnoea and the Shock Problem, *Bull. Johns Hopkins Hosp.* **21**:235 (Aug.) 1910.

The inhalation of carbon dioxide in connection with anesthesia was introduced by Henderson, Haggard and Coburn¹¹ as a means of stimulating breathing, particularly for the purpose of inducing rapid elimination of the anesthetic after operation. An even more important result of such inhalation is the prevention of postoperative atelectasis and pneumonia.

PNEUMONIA AFTER ASPHYXIA

Experience has demonstrated that the treatment for carbon monoxide asphyxia by the inhalation of a mixture of oxygen and carbon dioxide, as introduced by Henderson and Haggard¹² a few years ago, not only is effective in the relief of asphyxia and the removal of carbon monoxide from the blood, but has resulted also in a notable decrease of postasphyxial pneumonia.

The occurrence of râles, edema, bronchopneumonia and lobar pneumonia in patients who have survived carbon monoxide asphyxia without the inhalational treatment has been noted by a number of observers. Their observations were summarized by Hamilton¹³ in the statement that "evidence of injury to the lungs is shown in the fairly large proportion of the victims of gassing who have an excess of fluid in the respiratory tract." Drinker and Cannon¹⁴ found in 1923, before the inhalational treatment was introduced, that the hospital records were incomplete regarding such cases, but that they indicate the probability that some degree of bronchopneumonia must be present in nearly all patients who do not succumb immediately following asphyxia by city gas. In contrast, among many hundreds of patients, of whose cases we have reports, treated in recent years with the inhalation of oxygen and carbon dioxide, not a single case of subsequent pneumonia has occurred.

In experiments on dogs asphyxiated with carbon monoxide it was found that animals resuscitated by the inhalation of carbon dioxide make

11. Henderson, Y.; Haggard, H. W., and Coburn, R. C.: Administration of Carbon Dioxide After Anesthesia and Operation, *J. A. M. A.* **76**:672 (March 5) 1921. Henderson, Y.; Haggard, H. W., and Coburn, R. C.: Acapnia Theory, *J. A. M. A.* **77**:424 (Aug. 6) 1921.

12. Henderson, Y., and Haggard, H. W.: The Treatment of Carbon Monoxide Asphyxia by Means of Oxygen Plus Carbon Dioxide Inhalation, *J. A. M. A.* **79**:1137 (Sept. 30) 1922. Henderson, Y.: Resuscitation from Carbon Monoxide Asphyxia from Ether or Alcohol Intoxication, and from Respiratory Failure Due to Other Causes, *J. A. M. A.* **83**:758 (Sept. 6) 1924. Henderson, Y., and Haggard, H. W.: Noxious Gases, Chemical Catalog Co., 1925.

13. Hamilton, Alice: Industrial Poisons in the United States, New York, The Macmillan Company, 1925, p. 373.

14. Drinker, C. K., and Cannon, W. B.: Carbon Monoxide Asphyxia: The Problem of Resuscitation, *J. Indust. Hyg.* **4**:463, 1922-1923.

a complete recovery without pulmonary complications. On the other hand, in animals that are not thus resuscitated the lungs are found at autopsy to be "edematous, and the alveoli to be filled with an almost homogeneous coagulum of albumin-rich fluid. Vascular stasis is also marked in some cases, although there is only a slight cellular inflammatory reaction and a few widely scattered small hemorrhages."¹⁵

No attempt will be made here to explain how asphyxia induces such a condition in the lungs. It is sufficient for present purposes to note the fact that, both in experiments on animals and in observations on patients, inhalation of carbon dioxide, simultaneously with the relief of asphyxia by means of oxygen, counteracts the tendency for this condition to give rise to postasphyxial pneumonia.

ATELECTASIS IN PNEUMONIA

Atelectasis, or apneumatosi (Coryllos), known in the first half of the last century and then almost forgotten, was described again in 1908 and 1910 by W. Pasteur¹⁶ in cases of diphtheria with paralysis of the diaphragm. The clinical observations of Jackson and Lee¹⁷ showed that bronchial obstruction by preventing the ventilation of a part of the lung permits a gradual absorption of the air within its alveoli and thus results in the deflation and collapse of a lobe or lobules or of the whole of one lung. More than fifty years ago, experimental evidence was obtained by Mendelsohn¹⁸ and by Lichtheim¹⁹ that the insertion of a plug in a bronchus induces atelectasis in the portion of the lung to which it leads. But only recently has this subject been developed on the basis of thorough experimental investigation by Coryllos and Birnbaum.²⁰

They have devised plugs consisting of small rubber bags which are inserted in one of the main bronchi or in a branch by means of a bronchoscope and inflated so as to block off the airway completely. The dogs are narcotized with iso-amyl-ethyl barbituric acid to prevent coughing. Unilateral atelectasis develops in a few hours and is demonstrated by means of x-ray pictures. The most striking and most reliable index

15. Quoted from a report on autopsies, in 1922, by Dr. R. A. Lambert, department of pathology, Yale Medical School.

16. Pasteur, W.: Massive Collapse of the Lung, *Lancet* **2**:1351, 1908 and **2**:1080, 1910.

17. Jackson, Chevalier; and Lee, W. E.: Acute Massive Collapse of the Lungs, *Ann. Surg.* **82**:364 (Sept.) 1925.

18. Mendelsohn, A., quoted by Lord, F. F.: *Diseases of the Bronchi, Lungs and Pleura*, Philadelphia, Lea & Febiger, 1915.

19. Lichtheim, L.: *Arch. f. exper. Path. u. Pharmakol.* **10**:54, 1879.

20. Coryllos, Pol N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, *Arch. Surg.* **16**:501 (Feb.) 1928.

of the degree of atelectasis is afforded by displacement of the heart and mediastinum toward the side affected. The diaphragm is also elevated on that side and lowered on the side of the normal lung. In the dog the displacement of the heart is much greater than is possible in man, owing to the more rigid mediastinum in man, while the distortion of the diaphragm is greater in man than in the dog.

Following up this study of the effects of mechanical obstruction of the airways, Coryllos and Birnbaum² showed that lobar pneumonia is essentially a pneumococcic atelectasis. In their experiments, dogs which are deeply narcotized with iso-amyl-ethyl barbituric acid receive through the bronchoscope into one bronchus and its branches a small volume of a virulent culture of pneumococci concentrated by the centrifuge from a larger volume. The next day, a unilateral pneumococcic atelectasis with marked displacement of the heart toward the affected lung is found. This condition develops into a typical unilateral pneumonia with consolidation and hepatization. In the large majority of cases the disease terminates fatally in from one to three days.

Coryllos and Birnbaum also correlated this experimental evidence with clinical observations demonstrating that atelectasis is a critical factor in pneumonia. Thus, both experimental and clinical evidence indicates that in the development of pneumonia the first stage after infection is a catarrh which plugs the airways, great or small, with thick, sticky secretion and prevents their ventilation by the movements of respiration. The normal drainage is thus stopped, the air is absorbed, the lung or lobe or lobules are collapsed and an occluded area of infection is produced. In such areas, and only in such areas, pneumonia develops. The condition is sometimes successfully relieved in patients by aspirating the bronchi through a bronchoscope.

In pneumonia the heart is not displaced toward the normal lung, as it would be if the current conception were correct. In medical pneumonia, as in postoperative pneumonia, the heart is always displaced toward the pneumonic lung. This fact has now been observed also in pneumonia in children by Tallerman and Jupe.^{20a}

EXPERIMENTAL WORK

The Relief of Atelectasis.—The first series of experiments to be reported here was made for the purpose of determining the effectiveness of the inhalation of carbon dioxide in redilating a lung that had been collapsed by simple obstructive atelectasis without infection. In these experiments, twenty-four large dogs, from 12 to 25 Kg. in weight, were used. They received, by intraperitoneal injection, 0.5 cc. per kilogram of a freshly made 10 per cent solution of iso-amyl-ethyl bar-

20^a. Tallerman, K. H., and Jupe, M. H.: Displacement of Heart in Pneumonia in Childhood, *Arch. Dis. Childhood* 4:155 (Aug.) 1929, quoted in *J. A. M. A.* 93:1099 (Oct. 5) 1929.

bituric acid. Within fifteen minutes this induced, in nearly all cases, a deep narcosis lasting from twelve to twenty-four hours. An x-ray picture was taken to make sure that the heart and lungs were in normal condition and position. By means of a bronchoscope a rubber bag, similar to those used by Coryllos and Birnbaum but somewhat larger and fitted with a valve from a bicycle tire, was then inserted into the right bronchus and inflated with water so as to shut off as nearly as possible all the branches of the bronchus. In some of the earlier experiments a strong solution of sodium bromide or sodium iodide was used to inflate the bag; but it was found that if any of this solution escaped into the lung, it caused acute irritation or even immediate death. Water produces no such effect.

As soon as the bronchial plug was in place, the dog was laid in a special holder similar to that used by Coryllos and Birnbaum, so that its position could be adjusted as precisely as possible, and an x-ray picture was taken. The animal was then laid on its right side on the floor, where it remained in profound narcosis for many hours.

The next day, a second x-ray picture was taken and showed in all cases a degree of atelectasis and of displacement of the heart corresponding to the number of branches of the bronchus occluded; for atelectasis develops only in an area the airway of which is completely shut off. With the dog under ether anesthesia and by means of the bronchoscope the plug was withdrawn from the bronchus and the animal was placed in an atmosphere of air to which from 5 to 7 per cent of carbon dioxide was added. For this purpose a chamber 12 by 9 feet and 7 feet high (3.6 by 2.7 by 2.1 meters) was used. Its walls consisted of window sash; the joints were made airtight with soft asphalt. Beneath the wooden floor and above the wooden ceiling were layers of soft asphalt. It had double doors to form an air lock and was cooled by a coil of pipes (automobile radiator) connected to the main water supply of the laboratory and draining into a sink in the chamber. Carbon dioxide gas was run into this chamber from a cylinder of liquefied "carbonic acid" through a meter and was mixed with the air by an electric fan. The contents of the chamber were determined at intervals by gas analysis with an Orsat analyzer. Usually the initial concentration was about 7 per cent and dropped to 5 or 6 per cent in the course of an hour or two. From four to six animals were put into the chamber together and were allowed to move about freely. They breathed deeply but appeared comfortable and sometimes slept.

After the animals had been in the chamber from thirty to sixty minutes they were removed from it and another set of x-ray pictures was taken. These pictures were in striking contrast to those taken prior to the period in the chamber. They showed a restoration of a practically normal condition in the thorax.

The observations of Coryllos and Birnbaum²⁰ in earlier series of experiments have shown that simple obstructive atelectasis, such as these cases presented, usually clears up only in the course of several hours. It is therefore highly significant that after being in this chamber and inhaling carbon dioxide for only thirty to sixty minutes—shorter periods would probably have been sufficient—the atelectasis was in all cases relieved and the heart was restored to its normal position. These observations confirm experimentally the similar clinical observations of Scott and Cutler.⁵ The changes in the thorax, and particularly the displacement toward the atelectatic right lung of the line of the left

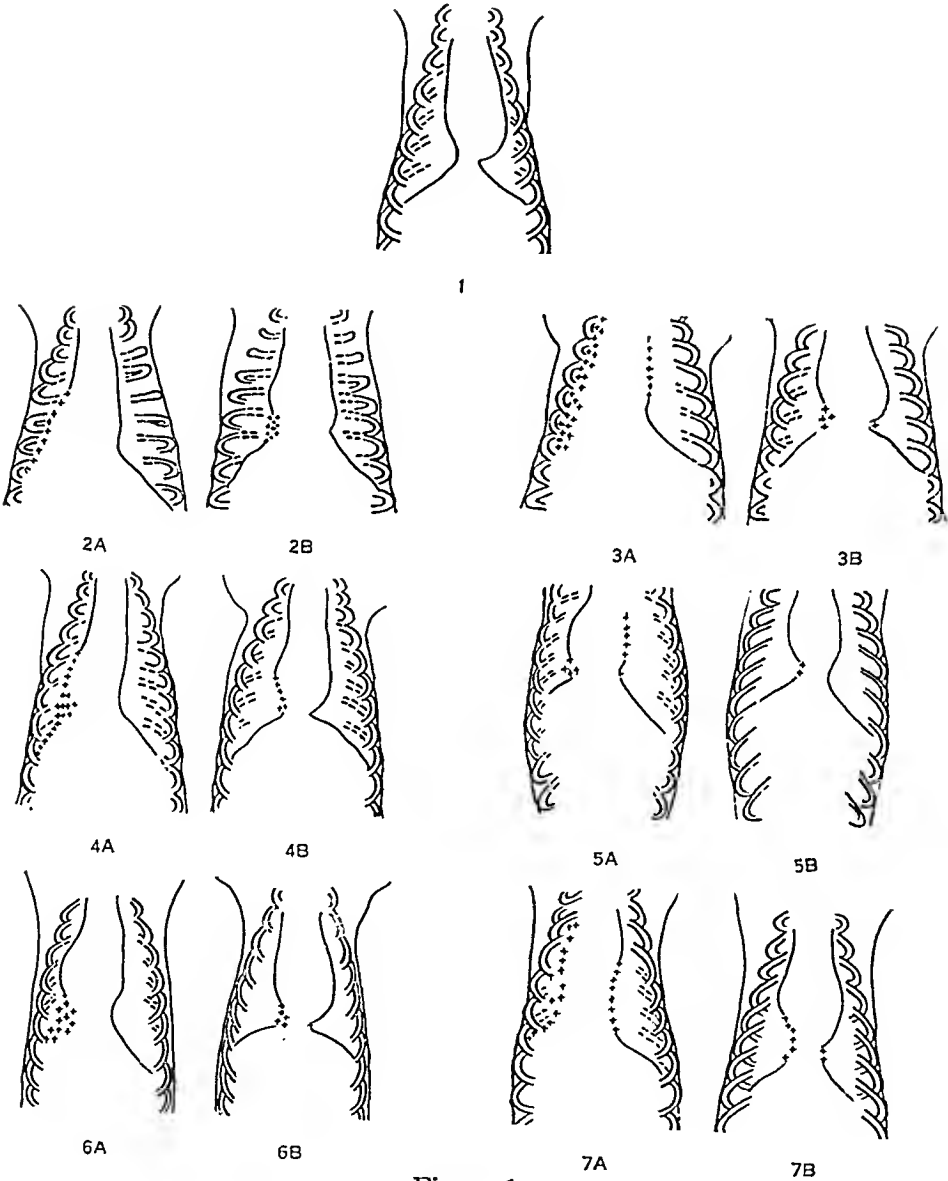


Figure 1

EXPLANATION OF FIGURE 1

Fig. 1.—Relief of atelectasis by inhalation of carbon dioxide (drawings traced from x-ray films): 1, outline of the normal thorax of a dog, weighing 15 Kg., showing the ribs, heart and diaphragm. Normal x-ray pictures were made from all the animals, but as all these pictures are essentially similar, only one is here reproduced. 2*A*, the thorax of dog AJJ, weighing 15 Kg., twenty-two hours after obstruction of the right common bronchus. Note the displacement of the heart, particularly of the left border (at the right in the drawing) away from the normal lung and toward the atelectatic lung. In this and succeeding pictures, cloudy outlines are indicated by ++++. 2*B*, after removal of the bronchial plug, the animal was kept in a chamber containing air and an average of 6 per cent carbon dioxide for fifty minutes. This picture was then taken. Note that the left border of the heart (at the right in the picture) has returned to nearly the normal position and that the right border of the heart (on the left in the picture) has a distinct outline through most of its extent and is in the normal position. 3*A*, the thorax of dog AL, weighing 26 Kg., twenty-one hours after obstruction of the right common bronchus. The right lung is almost completely collapsed and the heart is displaced, so that its left border is nearly in the mid-line. The right side of the diaphragm is obscured and the left side is distorted downward in a manner characteristic of contralateral atelectasis. 3*B*, after removal of the plug from the bronchus, the animal was kept under light ether anesthesia for twenty or thirty minutes during which time it struggled vigorously. This picture was then taken and shows that the atelectasis had almost completely cleared up, allowing the heart and diaphragm to return to their normal positions. The x-ray pictures, from which 3*A* and 3*B* are traced, are reproduced in figure 2. 4*A*, the heart of dog AJ, weighing 15 Kg., twenty-two hours after the right common bronchus was obstructed. The picture shows extreme atelectasis of the right lung with displacement of the heart and distortion of the diaphragm. 4*B*, after removal of the plug from the bronchus, the animal was placed for forty-five minutes in 6 per cent carbon dioxide; this picture was then taken. It shows that the atelectasis had cleared up and that the heart and diaphragm had returned to their normal positions. 5*A*, the thorax of dog AM, weighing 14 Kg., twenty-one hours after obstruction of the right common bronchus. There is atelectasis in the greater part of the right lung with displacement of the heart and distortion of the diaphragm. 5*B*, after removal of the plug from the bronchus the animal was placed in a chamber with 6 per cent carbon dioxide for forty minutes. The picture shows an almost complete return of the heart and diaphragm to the normal position. 6*A*, the thorax of dog AN, weighing 15 Kg., nineteen hours after obstruction of the right common bronchus. The extent of atelectasis in the right lung is indicated by the displacement of the heart and the distortion of the diaphragm. 6*B*, after removal of the plug from the bronchus, the animal was placed for forty minutes in 6 per cent carbon dioxide. At the end of this time, as the picture shows, the atelectasis had cleared up and the heart and diaphragm had returned to their normal positions. 7*A*, the thorax of dog AO, weighing 13 Kg., nineteen hours after obstruction of the right common bronchus. There is an extreme degree of atelectasis. 7*B*, after removal of the plug from the bronchus, the animal was placed for forty minutes in 6 per cent carbon dioxide. As the picture shows, the atelectasis at the end of this time had cleared up and the heart and diaphragm had returned to their normal position.

border of the heart, are shown for six experiments in figure 1. The significant details of the experiments are given in the legend.

As the bronchi are innervated by the vagi, three experiments were tried to determine whether these nerves may play a part in producing atelectasis. After the animal was narcotized, the right vagus was cut and the peripheral end stimulated; but no effects were observable in x-ray pictures after section or during stimulation. The bronchus was then plugged and atelectasis was developed precisely as in a lung with normal innervation. Next day, the atelectasis was relieved by the inhalation of carbon dioxide, precisely as in animals in which the nerve was not cut. These observations, so far as they go, indicate that the innervation of the lung is not involved in the production or relief of atelectasis, in agreement with Fontaine and Herrmann.²¹

Clear evidence that the main factor in redistending an atelectatic lung is deep breathing rather than the effects of carbon dioxide on the circulation, is afforded particularly by one experiment in which vigorous breathing was induced, after removal of the bronchial plug, by keeping the animal under light ether anesthesia for nearly half an hour. It struggled vigorously, and drew many deep breaths. In an x-ray picture taken immediately thereafter, the atelectasis had cleared up, while in the picture previous to this treatment the atelectasis was extreme. These pictures, shown in figure 2, afford conclusive evidence that it is deep breathing and not an effect of carbon dioxide on nervous or vascular mechanisms which clears up atelectasis.

The Relief of Pneumonia.—In this series of experiments, twenty-eight dogs were given the usual narcotizing dose of iso-amyl-ethyl barbituric acid. Prof. Leo F. Rettger supplied a virulent culture of pneumococcus type II from the Yale Laboratory of Bacteriology. A volume of 1.5 cc. of the culture per kilogram of body weight of the dog to be infected was centrifugated and decanted down to 0.2 cc. per kilogram of the animal's weight; the sediment was mixed in this volume. After insertion of the bronchoscope into the right bronchus, this concentrated suspension of pneumococci was insufflated into the bronchus and its branches.

After a preliminary group of experiments on six dogs, for practice in technic and procedure and for untreated controls, a series of experiments was carried out on twenty-two dogs. In this series, two dogs were found dead, chiefly from iso-amyl-ethyl barbituric acid poisoning, on the morning following narcotization, and four failed to develop pneumonia. Of the remaining sixteen all developed pneumonia—in most cases so severely that, judging by the six control animals and by the experience of Coryllos and Birnbaum, few if any would have survived. However, after spending various periods from two to twenty-four hours in from 5 to 7 per cent carbon dioxide in the chamber, all except three of the sixteen made a complete recovery. Even in those which died, autopsy showed that in two cases the cause of death was the suppurative pneumonitis, probably due to *Bacillus coli*, as was observed by Coryllos and Birnbaum, and as occurred also in some of our dogs a day or two after withdrawal of the bronchial plug in the preceding series of experiments.

More significant than such statistics, however, are the x-ray pictures, illustrations of which are given in figures 3 and 4, and outline drawings in figure 5. These figures and their legends show clearly: (1) that in all these cases of pneu-

21. Fontaine, R., and Herrmann, L. G.: Experimental Studies on Denervated Lungs, Arch. Surg. 16:1153 (June) 1928.

monia, atelectasis was a striking feature, and (2) that under inhalation of carbon dioxide a reinflation of the pneumonic lung occurred in all cases. It is noteworthy, however, that while in all respects, except one, these experiments on pneumonia and its relief appear closely similar to the preceding experiments on atelectasis without infection, in this one feature there is a significant difference between the two sets of experiments. Different times are required. While considerably less than one hour in an atmosphere of carbon dioxide was sufficient to overcome simple atelectasis due to a bronchial plug, two hours, and in some cases twenty-four hours, in this atmosphere was required to reinflate the pneumonic lung.

During the period of inhalation of carbon dioxide the dogs with pneumonia drank, or if too weak to drink by themselves, were assisted in drinking, large amounts of water. This probably aided in their recovery, by overcoming anhydremia.

COMMENT

The observations reported in the two foregoing sections taken together throw light on two important matters: (1) the part which

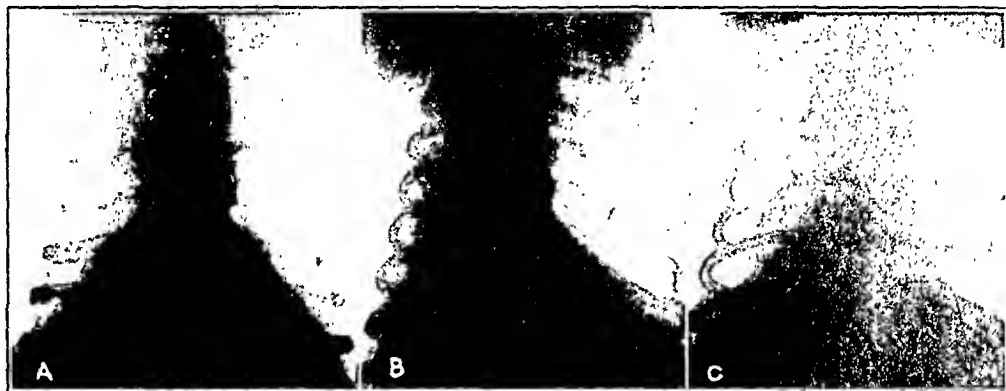


Fig. 2.—The thorax of dog AL: *A*, the normal condition, before the insertion of a plug in the right bronchus; *B*, extreme atelectasis the next day; *C*, half an hour later, reinflation of the right lung and restoration of the heart to the normal position, effected by removal of the plug and by a period of struggling and respiratory excitement under light ether anesthesia. The second and third of these pictures are also shown in outline as 3 *A* and *B* in figure 1.

atelectasis plays in pneumonia, and (2) the effectiveness of the inhalation of carbon dioxide as a prophylactic and therapeutic measure against pneumonia.

In relation to the first of these topics the outstanding feature of the observations reported is the similarity of the experiments on pneumonia to those on simple obstructive atelectasis. Not only are the x-ray pictures of atelectasis from bronchial obstruction and pneumonia from intrabronchial infection strikingly alike, but—even more significant—the effects of the inhalation of carbon dioxide in the two series of experiments are closely similar. There can scarcely be any doubt as to the general character of the process involved in the opening up of a lung rendered atelectatic merely by bronchial obstruction without infection.

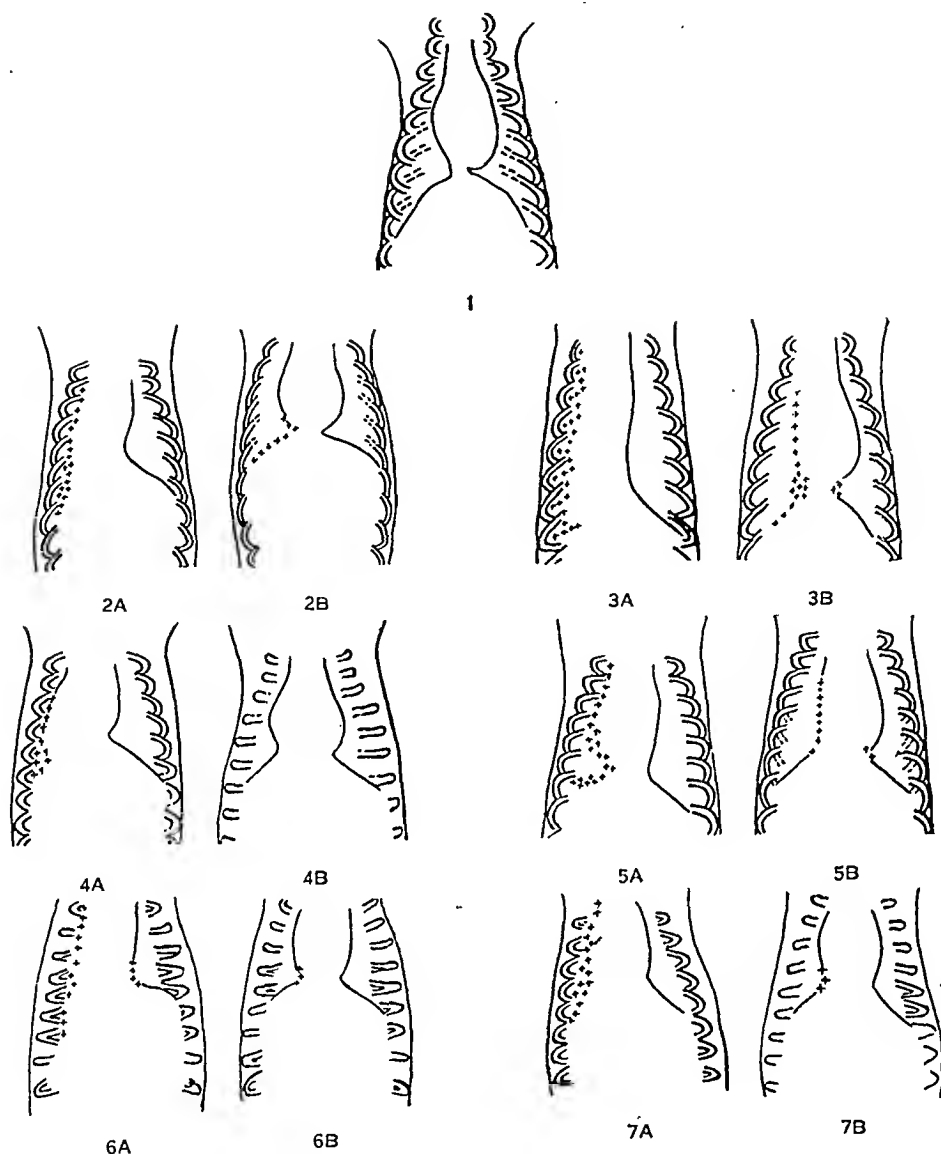


Fig. 3.—Relief of pneumonia by inhalation of carbon dioxide (drawings traced from x-ray films): 1, outline of the normal thorax of a dog, weighing 17 Kg., showing the ribs, heart and diaphragm. This will serve for comparison with the pictures of pneumonia indicated as *A* and of recovery indicated as *B* in the subsequent pictures. 2 *A*, the thorax of dog PE, weighing 12 Kg., twenty-four hours after insufflation of 6 cc. of the sediment concentrated by the centrifuge from 18 cc. of a culture of pneumococci type II. Note the displacement of the heart toward the pneumonic lung, indicating extreme collapse of the right lung, which was nearly as opaque to x-rays as the heart was. In this and succeeding pictures, cloudy outlines are indicated by ++++. 2 *B*, the animal was placed in carbon dioxide, of an average concentration of 6 per cent, but showed only slight improvement during the first two hours. After twenty-three hours, however, the pneumonia had to a large extent cleared up and this picture was obtained. The animal made a complete recovery. It was killed four days later and when it underwent autopsy the lungs were found normal. The x-ray pictures, from

EXPLANATION OF FIGURE 3—Continued

which 2 *A* and 2 *B* are traced, are reproduced in figure 4. 3 *A*, the thorax of dog PF, weighing 17 Kg., twenty-four hours after insufflation of the sediment concentrated from 25 cc. of the culture of pneumococci. Note the extreme displacement of the heart; the left hand border is almost on the line of the vertebral column. A large part of the right lung was as opaque to x-rays as the heart itself. 3 *B*, the animal was placed in carbon dioxide, average concentration of 6 per cent, for two hours, after which this picture was taken. There is an almost complete restoration of the heart to the normal position, but an incomplete clearing up of the lung. The animal was extremely ill and died two hours later. At autopsy considerable areas in the right lung and a part also of the left lung were found to be hepatized. 4 *A*, the thorax of dog PG, weighing 20 Kg., twenty-four hours after insufflation of the sediment concentrated from 30 cc. of the culture of pneumococci. There is an intense unilateral pneumonia with displacement of the heart toward the infected lung. 4 *B*, the animal was placed in carbon dioxide, average concentration 6 per cent, but made only slight improvement during the first few hours. After twenty-four hours in decreasing concentrations of carbon dioxide from 7 to 4 per cent the picture was taken from which this drawing is traced. It shows that the right lung had largely cleared up, and that the heart had returned to nearly the normal position. The animal appeared entirely well the next day. It was killed and underwent autopsy four days later. The lungs were found normal except for a few small areas of congestion in the upper lobe of the left lung. 5 *A*, the thorax of dog PJ, weighing 17 Kg., twenty-four hours after insufflation of the sediment from 25 cc. of the culture of pneumococci. There is displacement of the heart to the right and opacity of the right lung except on its costal border. 5 *B*, the animal was placed in carbon dioxide, average concentration 6 per cent, for one and three-fourths hours. This picture was then taken and shows restoration of the heart to a nearly normal position, and a considerable degree of clearing in the right lung. The animal was found dead the next day. On autopsy it was found to have developed a suppurative pneumonitis with a strong fecal odor, probably due to infection by *Bacillus coli*. 6 *A*, the thorax of dog PS, weighing 14 Kg., twenty-three hours after insufflation of the sediment from 21 cc. of the culture of pneumococci. There is displacement of the heart to the right and complete opacity at the right lung except along the costal margin. 6 *B*, after two hours in carbon dioxide, average concentration 6 per cent, the heart had returned about half way to normal position and the right lung had cleared to a considerable extent, as shown. Before being placed in the chamber this dog showed a rectal temperature of 101 F. After two hours in carbon dioxide its temperature was 99.8 F. The animal appeared entirely well the next day, and was alive and healthy two weeks later. 7 *A*, thorax of dog PT, weighing 20 Kg., twenty-three hours after insufflation of the sediment from 30 cc. of the culture of pneumococci. There is displacement of the heart to the right, disappearance of the outline of the right side of the heart and of the right side of the diaphragm and a high degree of congestion in the right lung. 7 *B*, after two hours in carbon dioxide, average concentration 6 per cent, the heart had returned to nearly normal position and the right lung had largely cleared, as shown. The rectal temperature before the animal was placed in the carbon dioxide chamber was 102.8 F. At the end of the two hours of inhalation the temperature was 101.2 F. This dog made an uneventful recovery and was alive and well two weeks later.

Therefore the fact that inhalation of carbon dioxide results in a closely similar, even if much slower, opening up of a pneumonic lung affords conclusive proof that atelectasis is a factor in pneumonia. This conclusion is further reinforced by the fact that dogs with pneumonia, which would otherwise prove fatal, are generally restored to health as a consequence of this reopening of the lung. That pneumonia derives its virulent character to a large degree from the fact that it is an occluded infection is also thus proved; for the chief effect of opening up the pneumonic lung under inhalation of carbon dioxide is to provide drainage, although there may also be chemical and bactericidal effects, and influences on the circulation. Once it is reopened the lung may clear itself. As in many surgical infections, so in medical pneumonia, occlusion is the critical morbidic factor. Thus, the thesis of Coryllos and Birnbaum that lobar pneumonia is a pneumococcic atelectasis is completely confirmed.

On the second topic, the effectiveness of inhalation of carbon dioxide as a prophylactic measure against pneumonia, these observations are equally conclusive. The reason that the treatment of carbon monoxide asphyxia by inhalation of oxygen and 5 per cent carbon dioxide prevents a subsequent pneumonia—a fact which we have known for several years but could not previously explain—is now clear. Similarly, the discovery of Scott and Cutler and of German surgeons that inhalation of carbon dioxide at the termination of general anesthesia prevents post-operative pneumonia is confirmed and explained. The value of inhalation of carbon dioxide in the treatment of asphyxia and in connection with anesthesia is shown to be far greater than originally claimed by Henderson and Haggard. They introduced this treatment as a means of stimulating respiration and thus hastening the elimination of carbon monoxide, the anesthetics, and other foreign and toxic volatile substances from the blood. The accessory effect of preventing pneumonia after anesthesia and operation and after asphyxia is more important. If this inhalation proves even partially effective in the treatment of medical pneumonia, that result will become of yet greater importance.

Several hundred patients with pneumonia have been treated with oxygen and 5 per cent carbon dioxide by means of the inhalators employed in resuscitating patients with carbon monoxide asphyxia. In one group of 126 cases, the report shows that only nine patients died, while a number recovered by crisis immediately after the inhalation. Even more important than this low mortality is the fact that of the patients treated early nearly all recovered, while the deaths were nearly all among those treated late. In a much larger group of patients not so treated the mortality was 31 per cent. These observations are to be continued and will be reported in a later paper.

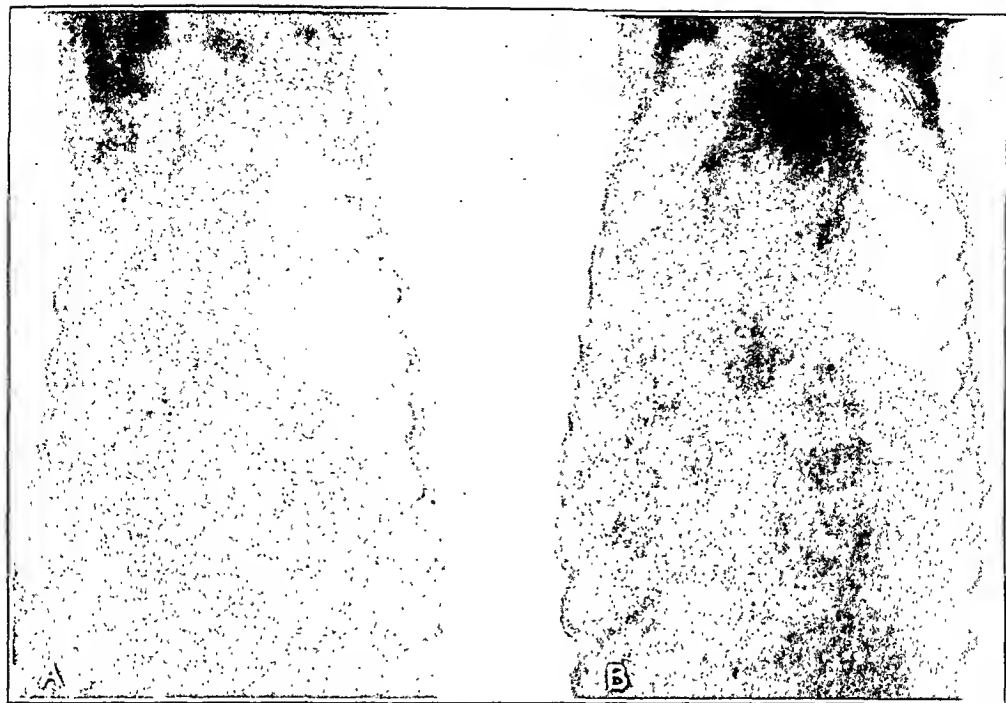


Fig. 4.—*A* shows unilateral pneumonia in dog PE, twenty-four hours after insufflation of pneumococci type II into the right bronchus; *B*, restoration of the heart to the normal position and partial clearing up of the pneumonic right lung after twenty-three hours in 6 per cent carbon dioxide. This animal made a complete recovery. It was killed and underwent autopsy four days later; the lungs were found to be normal. These pictures are also shown in outline in 2 *A* and *B* in figure 3.



Fig. 5.—*A* shows unilateral pneumonia in dog PF, twenty-four hours after insufflation of pneumococci type II into the right bronchus; *B*, restoration of the heart to the normal position and partial clearing of the pneumonic right lung after inhalation of 6 per cent carbon dioxide for two hours. The animal was extremely ill and died two hours later. These pictures are shown in outline in 3 *A* and *B* of figure 3.

PHYSIOLOGIC EVIDENCE IN ATELECTASIS

Atelectasis presents a number of puzzling subsidiary problems. Is the causation of atelectasis wholly mechanical, as Coryllos and Birnbaum concluded from their investigations? Or, on the other hand, are there nervous and vascular factors in the collapse of the lung? How are the gases, particularly nitrogen, absorbed? Is there any connection between this problem and that of the spontaneous reinflation of the lung after a therapeutic pneumothorax? Is the difference between pneumothorax and atelectasis wholly dependent on the patency or obstruction of the airways? What light does the evidence from the anatomy of the lung and from the experimental physiology of the bronchial innervation throw on these questions?

The physiologic literature affords little help in understanding these problems. We refer to this literature here chiefly in order to be of service to any reader who may wish to consult it in the hope of finding some hint that others have missed. On the anatomic side the excellent recent review by Macklin²² gives a picture of the lung as a contractile organ permeated with nonstriated muscle tissue. This conception is certainly suggestive. On the side of the physiology of the lung the extensive investigations of Carlson and Luckhardt²³ and the observations of Patterson²⁴ show that, if the lungs of men and of frogs were entirely alike, the explanation of atelectasis would probably be found in a nervous effect induced through the vagi and resulting in a prolonged contraction of the intrinsic musculature of the lung. This phenomenon, as described by these investigators in the frog, has not, however, been produced experimentally in a mammal.

The literature on the nervous control of the bronchi in mammals has usually had as its background the phenomena of asthma, as in the paper of Mount,²⁵ and the pharmacologic relief of the symptoms of that disorder; it helps but little toward an understanding of atelectasis. The long papers of Einthoven²⁶ and of Beer²⁷ are the classics in this field.

22. Macklin, C. C.: The Musculature of the Bronchi and Lungs, *Physiol. Rev.* **9**:1 (Jan.) 1929.

23. Carlson, A. J., and Luckhardt, A. B.: Studies on the Visceral Sensory Nervous System, *Am. J. Physiol.* **54**:55 (Nov.) 1920; **55**:13 and 31 (Feb.), 212 (March), 366 (April); **56**:72 (May); **57**:299 (Sept.) 1921.

24. Patterson, T. L.: Studies on the Visceral Sensory Nervous System: IX. The Readjustment of the Peripheral Lung Motor Mechanism After Bilateral Vagotomy in the Frog, *Am. J. Physiol.* **58**:169 (Nov.) 1921.

25. Mount, H. T. R.: Experimental Study of the Effects of Stimulation and Section of the Vagal Innervation to the Bronchi, and Their Possible Relation to Asthma, *Am. J. M. Sc.* **177**:697 (May) 1929.

26. Einthoven, W.: Ueber die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht und über Asthma nervosum, *Arch. f. d. ges. Physiol.* **51**:367, 1892.

27. Beer, Theodor: Ueber den Einfluss der peripheren Vagusreizung auf die Lunge, *Arch. f. Anat. u. Physiol.*, 1892, p. 101.

The work of Haldane²⁸ and his collaborators comes closer to suggestions of importance than that of most other investigators. It shows that shallow breathing in a normal man may leave considerable areas of the lung unventilated, as evidenced by cyanosis. Doubtless a continuation of the experiment and some accumulation of mucus to form a plug in an air tube would produce atelectasis.

Dunn,²⁹ and Binger and his collaborators³⁰ have demonstrated that multiple small emboli experimentally introduced into the pulmonary circulation may induce shallow breathing. Porter and Newburgh³¹ showed that irritation of the afferent endings of the vagi in the lungs is the cause of the shallow, rapid breathing in pneumonia. Churchill and Cope³² gave a similar demonstration for pulmonary congestion and edema. Shallow breathing, according to Meakins,³³ is in turn the cause of anoxemia in pneumonia, for it ventilates the lungs incompletely. All the factors of a vicious circle are thus provided.

Among the papers dealing with the pharmacologic aspects of the bronchi and their innervation, those of Dixon,³⁴ Trendelenburg³⁵ and Tiefensee³⁶ are especially noteworthy. Reviews giving the physiologic

28. Haldane, J. S.: *Respiration*, New Haven, Conn., Yale University Press, 1922, p. 136.

29. Dunn, J. S.: *The Effects of Multiple Emboli in Pulmonary Arterioles*, *Quart. J. Med.* **13**:129, 1920.

30. Binger, A. L.: *Experimental Studies on Rapid Breathing: II. Tachypnea, Dependent upon Anoxemia, Resulting from Multiple Emboli in the Larger Branches of the Pulmonary Artery*; *J. Clin. Investigation* **1**:155 (Dec.) 1924. Binger, A. L., and Moore, R. L.: *J. Exper. Med.* **45**:655, 1927.

31. Porter, W. T., and Newburgh, L. H.: *Am. J. Physiol.* **42**:175, 1916; **43**:455, 1917. Porter; Newburgh and Means, J. H.: *J. Exper. Med.* **24**:583, 1916.

32. Churchill, E. D., and Cope, O.: *The Rapid Shallow Breathing Resulting from Pulmonary Congestion and Edema*, *J. Exper. Med.* **49**:531, 1929.

33. Meakins, J.: *Harmful Effects of Shallow Breathing with Special Reference to Pneumonia*, *Arch. Int. Med.* **25**:1 (Jan.) 1920.

34. Dixon, W. E., and Brodie, T. G.: *Contributions to the Physiology of the Lungs: I. The Bronchial Muscles, Their Innervations and the Action of Drugs upon Them*, *J. Physiol.* **29**:97, 1903. Dixon, W. E., and Ransom, F.: *Bronchodilator Nerves*, *J. Physiol.* **45**:413, 1913. Dixon, W. E., and Hoyle, J. C.: *Studies in the Pulmonary Circulation: I. The Vaso-Motor Supply*, *J. Physiol.* **65**:299 (June 24) 1928. Dixon, W. E., and Hoyle, J. C.: *Studies in the Pulmonary Circulation: II. The Action of Adrenalin and Nicotine*, *J. Physiol.* **67**:77 (Feb. 28) 1929.

35. Trendelenburg, P.: *Physiologische und pharmakologische Untersuchungen an der isolierten Bronchialmuskulatur*, *Arch. f. exper. Path. u. Pharmakol.* **69**:79, 1912; *Versuche an der isolierten Bronchialmuskulatur*, *Zentralbl. f. Physiol.* **26**:1, 1913.

36. Tiefensee, K.: *Pharmakologische Studien auf der Bronchialmuskulatur: I. Methodik*, *Arch. f. exper. Path. u. Pharmakol.* **139**:129, 1929. II. *Ueber die Bedeutung der Blutbeschaffenheit für den Tonus der Bronchialmuskeln und ihr Ansprechen auf Gifte* **139**:139, 1929.

and pharmacologic literature have been published by Starling in Schafer's Textbook of Physiology,³⁷ by Boruttau in Nagel's handbook,³⁸ Schenck in Tigerstedt's handbook,³⁹ and Skramlik⁴⁰ in volume 2 of the excellent handbook now under publication, edited by Bethe and others. Volume 2 of this handbook also contains monographs dealing with the anatomy of the lungs by Felix,⁴¹ the mechanics of respiration by Rohrer,⁴² the chemistry of the respiratory exchange by Liljestrand,⁴³ the pathologic physiology of the airways by Amersbach,⁴⁴ the pathologic physiology of respiration by Hofbauer⁴⁵ and the pharmacology of respiration by Bayer.⁴⁶

A survey of all this literature affords, however, little direct evidence that atelectasis can arise directly from nervous influences on the lung. At present, the only clearly demonstrated causes are shallow breathing and the accumulation of mucus, resulting in the mechanical blocking of the air tubes.

SUMMARY AND CONCLUSIONS

1. As the background for this study, the following facts are cited:

(a) If the lungs are not fully distended soon after birth, pneumonia is likely to develop.

(b) After surgical operations, massive, lobar or lobular atelectasis of the lung is a rather frequent occurrence, and is the condition from which postoperative pneumonia develops. This atelectasis or, better, apneumotosis is prevented and relieved, and the risk of pneumonia is eliminated, by the inhalation of carbon dioxide.

37. Starling, E. H.: The Muscular and Nervous Mechanism of the Respiratory Movements, Text-book of Physiology, vol. 2, New York, The Macmillan Company, 1900, p. 274.

38. Boruttau, Heinrich: Die Atembewegungen und ihre Innervation: IV. Die Innervation der Atembewegungen, in W. Nagel: Handbuch der Physiologie des Menschen, Braunschweig, F. Vieweg und Sohn, 1909, vol. 1, p. 29.

39. Schenck, F.: Atembewegungen, Handbuch der physiologischen Methodik, vol. 2, Leipzig, 1908.

40. Von Skramlik, Emil: Die Physiologie der Luftwege, Handbuch der normalen und pathologischen Physiologie, ed. by Bethe, Bergmann Embden and Ellinger, Berlin, Julius Springer, 1925, vol. 2, p. 128.

41. Felix, Walther: Anatomie der Atmungsorgane, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 37.

42. Rohrer, Fritz: Physiologie der Atembewegung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 70.

43. Liljestrand, G.: Chemismus des Lungengaswechsels, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 190.

44. Amersbach, K.: Patho-Physiologie der Luftwege, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 307.

45. Hofbauer, Ludwig: Pathologische Physiologie der Atmung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 337.

46. Bayer, Gustav: Pharmakologie der Atmung, Handbuch der normalen und pathologischen Physiologie, vol. 2, p. 455.

(c) The inhalation of 5 per cent carbon dioxide in oxygen, which is now the standard treatment for carbon monoxide asphyxia, is also an effective preventive of postasphyxial pneumonia.

(d) In pneumonia it is the blocking of the lung airways, bronchi or bronchioli, by plugs of thick and sticky secretion which is the critical morbidic factor producing atelectasis and the conditions characteristic of an undrained infection.

2. The experiments here reported demonstrate these facts:

(a) Atelectasis that is induced experimentally in dogs by blocking a bronchus is quickly cleared up and the lung is redistended by the deep breathing induced by inhalation of carbon dioxide in proper dilution.

(b) Pneumonia that is induced in dogs by insufflation of a virulent culture of pneumococci is generally overcome, the lung is redistended and the animal is restored to health by inhalation of carbon dioxide sufficient to cause deep breathing and continued until the pneumonic area is cleared.

3. Success with this therapy for the relief of pneumonia in patients depends on administering the inhalation as early as possible. If medical pneumonia is thus treated early enough, it appears probable that the results may be as effective as those already attained in postoperative and postasphyxial pneumonia.

NOTE.—The second paper of this series will deal with the chemical and bactericidal effects of inhalation of carbon dioxide.

ATELECTASIS IN THE PATHOGENESIS OF ABSCESS OF THE LUNG

A STUDY OF SPONTANEOUS PULMONARY SUPPURATION IN THE
ALBINO RAT *

THEODORE S. MOISE, M.D.

AND

ARTHUR H. SMITH, PH.D.

NEW HAVEN, CONN.

Although numerous observations have been made on pulmonary infection in the albino rat, definite knowledge concerning the etiologic agent and the factors in the pathogenesis of this disease is lacking. The lesions of the lungs vary greatly according to the stage and extent of the process, but the essential nature of the completely developed lesions is that of chronic pulmonary suppuration. The late stages of the disease are frequently misnamed "pneumonia," while the earlier manifestations of the condition are imperfectly understood. The purpose of the present communication is to present a series of observations which suggest that atelectasis subsequent to bronchial occlusion is a primary factor in the development of this disease.

The literature contains numerous assertions on the one hand that the lungs are sterile, and on the other hand that they frequently contain micro-organisms. Thomson and Hewlett¹ estimated that 1,500 organisms or more were taken into the air passages per hour in London and claimed that the ciliary action of the lining epithelium soon rids the inspired air of organisms. In addition to the action of the cilia, there is the important mechanism of phagocytosis in removing organisms from the respiratory tract.

The probable pathway of infection has been indicated in a study of the occurrence and source of the micro-organisms in the lungs of normal animals (Jones).² In not a single instance did all of the culture tubes inoculated with the lungs from guinea-pigs, rabbits and calves remain sterile, but in the mouse and the rat the proportion of positive

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* From the Department of Surgery and the Laboratory of Physiological Chemistry, Yale University.

* A preliminary report has been made in the Proceedings of the Society of Experimental Biology and Medicine **26**:723, 1929.

1. Thomson, St. C., and Hewlett, R. T.: *Lancet* **1**:86, 1896.

2. Jones, F. S.: *J. Exper. Med.* **32**:361, 1922.

cultures was much lower. It seemed probable to Jones that the high percentage of positive cultures in the herbivorous animals was due to the relatively larger number of organisms in the environmental atmosphere of these animals, probably originating from the hay and straw which form their diet. In further studies he was able to show that the number of positive cultures could be raised or lowered in proportion to the relative amount of dust in the atmosphere in which the animals were maintained. These observations have a practical bearing in the study of spontaneous and experimental pulmonary disease in animals. Although the organisms obtained were nonpathogenic, there is no reason to doubt that animal pathogens do gain an entrance in this manner.

The literature contains reports of numerous instances in which organisms have been isolated from the lungs of rats suffering from pulmonary infection. Klein³ and Mitchell⁴ have cultivated a granular gram-positive bacillus. This organism was named *Bacillus muris* by Klein. A streptothrix from the lungs of twenty rats was cultivated by Tunnicliff,⁵ who also obtained a variety of other organisms (strep-tococci, staphylococci, pneumococci, diphtheroid bacilli, colon bacilli, etc.). Hoskins and Stout⁶ obtained *Bacillus bronchisepticus* from the upper respiratory tract and lungs of rats suffering from pulmonary infection. Jones⁷ isolated *B. actinoides* in eleven instances and *B. bronchisepticus* and a streptothrix from a few animals. The results of the bacterial cultures do not permit a definite conclusion as to the etiologic organism of pulmonary infection in white rats. In fact, they suggest that a variety of organisms may be involved.

The anatomic characteristics of the pulmonary lesions have been described by Hektoen⁸ in the following words:

Two main types of lesions may be distinguished. In one the affected tissue, most often part or parts of one or more lobes, is solid and red, usually with more or less well marked nodular areas of reddish-yellow or yellowish color; on the cut surface and in the microscopic sections such areas correspond with accumulations of exudate, which is mostly cellular, within the bronchial system, and in the earlier stages the consolidation of the tissue proper is due to cellular exudate in the alveoli with congestion associated with collapse. This is probably the more common lesion. In a few instances an entire lobe is found uniformly solid throughout, deeply congested and red or reddish-gray in color; rarely we have found more or less uniform congestion in one or more lobes with much mucus in the bronchi. In what may well be later stages of the bronchopneumonic process, the lungs are found "riddled with abscesses" with thick yellow pus; some

3. Klein, E.: *Centralbl. f. Bakteriol.* **33**:488, 1903.

4. Mitchell, O. W. H.: *J. Infect. Dis.* **10**:17, 1912.

5. Tunnicliff, R.: *J. Infect. Dis.* **19**:767, 1916.

6. Hoskins, H. P., and Stout, A. L.: *J. Lab. & Clin. Med.* **5**:307, 1919-1920.

7. Jones, F. S.: *J. Exper. Med.* **36**:329, 1922.

8. Hektoen, L.: *Tr. Chicago Path. Soc.* **10**:105, 1916.

of these appear to lie in bronchial dilatations, while others may have dense fibrous capsules.

In the second type of lesion districts of lung tissue, frequently with sharp but irregular margins, appear somewhat gelatinous, largely homogeneous, even translucent, light-gray or reddish-gray, though often with more opaque yellowish spots. The gelatinous appearance corresponds with mucoid degeneration of the bronchopneumonic exudate, and it may be associated with connective tissue proliferation, the mucoid material then usually appearing dense and inspissated.

These two main types of lesion may be present in the same lungs and in the same lobe, and individual lesions occur which appear to partake of the characteristics of each type. The difference between the two types would seem to depend on the predominance of suppuration in the one and of mucoid change in the other.

As a rule in well-marked cases the bronchi and the trachea contain much turbid, viscid mucus.

Special mention must be made of certain sharply defined, solid, deeply red areas, usually at the tips of lobes, which look very much like red infarcts, but are caused apparently by collapse of lung tissue due to occlusion of bronchi either by exudate or through fibrous obliteration. Then there are pure vesicle-like lesions, usually minute subpleural as well as deep, with clear, colorless mucoid contents, apparently formed by accumulation of mucus and mucoid material in bronchi and other spaces.

Usually the pleura is free and smooth; over large chronic abscesses there may be adhesions; occasionally scars are found and deposits of coal dust occur.

The studies mentioned in the foregoing paragraphs have made valuable contributions to the knowledge of pulmonary disease in the albino rat. The probable pathway of infection is suggested (Jones)⁸ and the anatomic studies (Hektoen⁸) are complete, but the exact etiologic agent is obscure and the existing literature does not explain the pathogenesis of the disease. It is on the latter question, namely the mechanism of the condition, that our own observations and interpretation are significant.

EXPERIMENTAL WORK

Source of Material.—Most of the animals on which the present observations are based were used in an extensive dietary experiment. The others were obtained from miscellaneous sources. It is possible, therefore, to draw a correlation between the incidence and severity of the lesions and the level of the protein in the ration, the only variable in the experimental food. All the diets were adequate. Atelectasis and frank infection occurred irrespective of the diet fed.

Method.—The method of study has been to remove the intact trachea and lungs from a large number of rats and to make observations on the gross and microscopic anatomy. In certain instances the bronchi leading to affected areas were injected or dissected out, and in others corrosion specimens of the bronchial tree were prepared.

Observations.—The normal lung in the rat consists of a single large left lobe, an upper, middle and lower right lobe and an infracardiac

lobe. The latter lobe is a part of the right lung. In a few instances anomalous lobes were observed.

The lesions of the lungs vary greatly according to the stage and the extent of the process, but the essential nature of the completely developed disease is that of chronic abscesses of the lung. There are several main types of anatomic change representing different stages in the condition. The earliest and probably the commonest easily recognizable change is that of atelectasis. The affected part may be a small shrunken, solid, red collapsed area at the periphery of a lobe or a similar area involving an entire lobe or in some instances more than half of the entire area of the lung (figs. 1 and 2). If the process is



Fig. 1.—Obstructive atelectasis of the tip of the infracardiac lobe of the rat's lung. There is no evidence of infection. The remaining lobes are normal; $\times 2$.

extensive, the uninvolved lobes are emphysematous. In this stage of the condition there is no gross or microscopic evidence of infection in the pulmonary parenchyma.

The second stage of the lesion shows areas with sharp irregular margins that appear as pearly-gray semitranslucent nodules at the edge of a lobe or situated within an atelectatic area. On cross-section these nodules contain a gelatinous mucoid substance. In some instances there is at this stage no evidence of abscess formation. The bronchi frequently contain accumulations of mucus in association with the two types of change described in the foregoing.

In the final stages of the disease, that of the well developed abscess, the lungs show multiple discrete or confluent yellow opaque nodules (fig. 3). On section, these areas contain thick yellow or greenish-yellow pus. In some instances the confluence of the individual abscesses produces a single large nodular mass occupying a major part of the thoracic cavity. A majority of the abscesses are situated within bronchial dilatations; others are apparently completely surrounded by dense fibrous capsules (fig. 4).

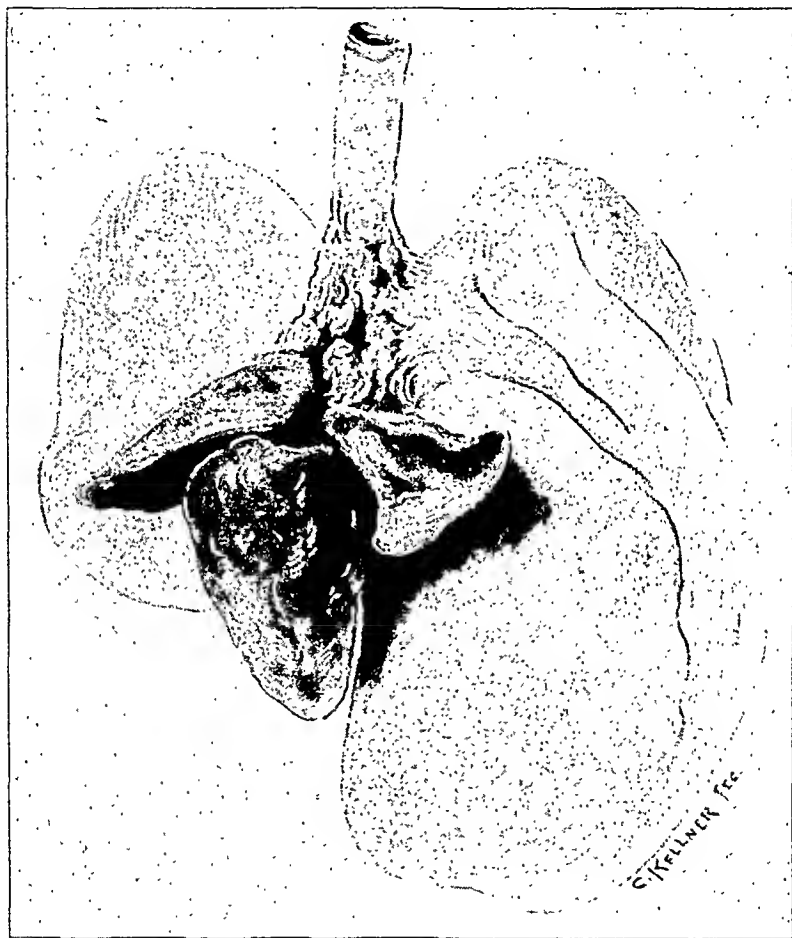


Fig. 2.—Obstructive atelectasis of the right middle, lower and infracardiac lobes. There is no evidence of infection. The right upper and the left lobes show a compensatory emphysema. Reduced from a magnification of $\times 2$.

The pleural cavity is rarely invaded but with the large confluent abscesses it is frequently partly obliterated by adhesions. In one instance, a purulent pleurisy and pericarditis were observed. In another animal there was a purulent pericarditis with marked dilatation of the pericardial cavity and thickening of the pericardium. There was no evidence of infection in any of the other organs of the rats studied.

By injection and dissection of the bronchial tree, points of occlusion of the bronchi leading to the atelectatic areas have been demonstrated (fig. 5). In this manner mucous plugs completely occluding the bronchial lumina were observed just proximal to the collapsed areas. In some instances, the minute size of the bronchi precluded the demonstration of such plugs, although there is no doubt concerning the obstructive nature of the atelectasis.

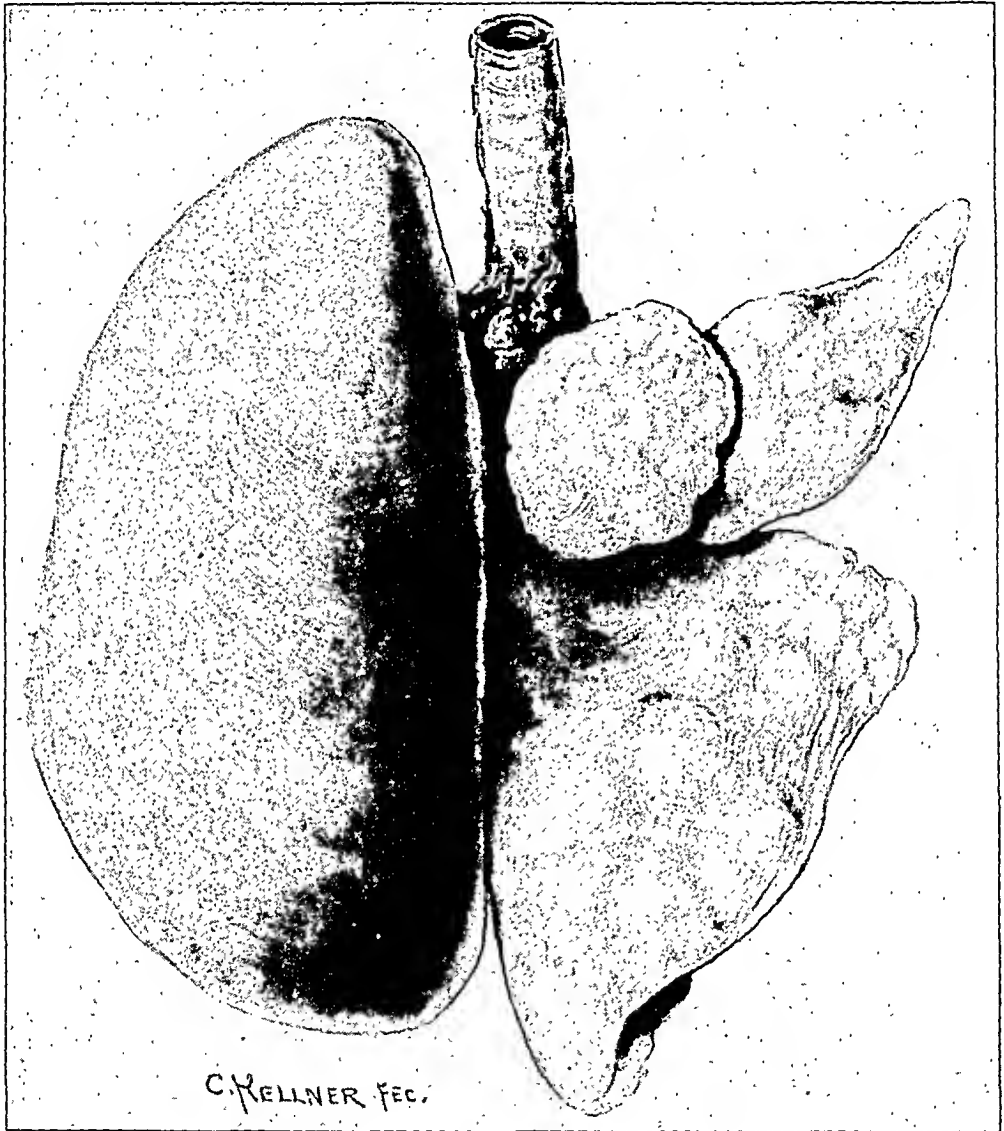


Fig. 3.—The right upper lobe shows multiple small abscesses superimposed on an atelectasis. The right middle and lower lobes show multiple larger abscesses. These lobes are not collapsed. The left lobe is normal. Reduced from a magnification of $\times 2$.

A detailed study of microscopic sections confirmed the foregoing observations on the gross anatomy. In the early atelectatic stage of the disease the pulmonary parenchyma is collapsed (fig. 6). There is no alveolar or bronchial exudate. In an apparently later stage, accumu-

lations of an amorphous noncellular material (mucus) are observed within dilated bronchi, and in still later stages a thick purulent exudate, containing a variable quantity of mucus. The sections also show that many of the abscesses are within bronchiectatic cavities; others are encapsulated by a dense fibrin band. In some sections the bronchiectatic abscess cavities are lined by normal bronchial columnar epithelium; in others the lining cells are of the pavement type, and in some areas no epithelial cells are observed.

The exudate within the lung tissue is largely peribronchial in distribution. In fact, there is little if any evidence of a "pneumonia" except

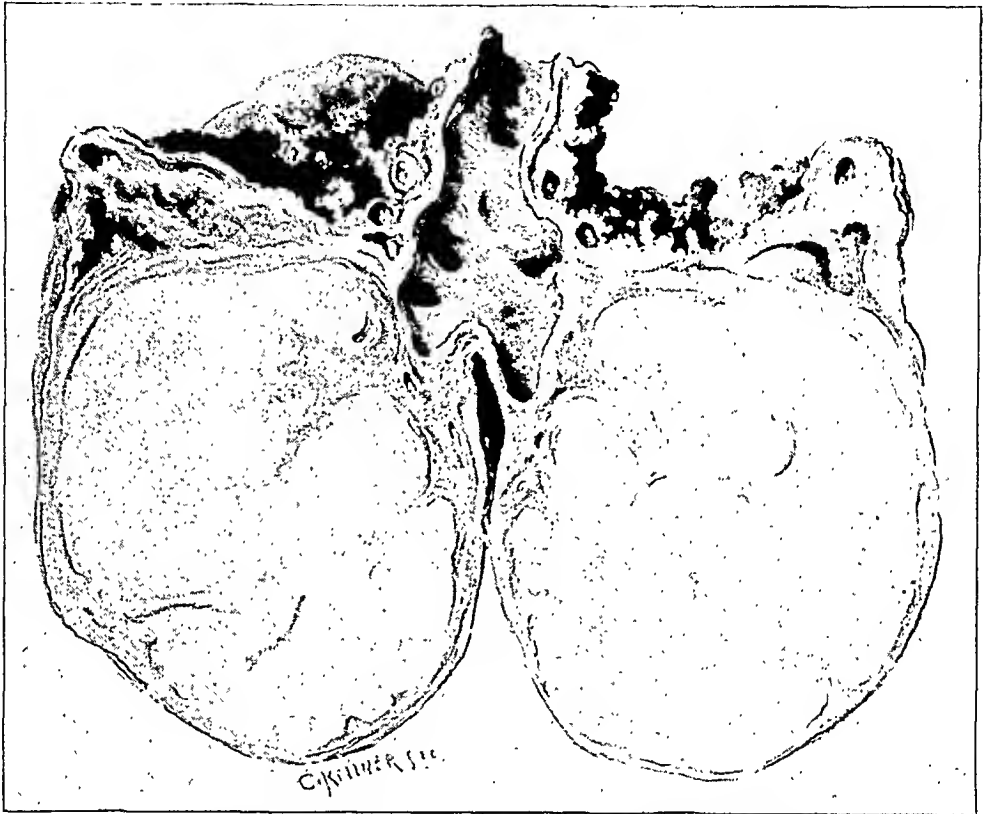


Fig. 4.—The drawing shows a large bronchiectatic abscess; $\times 2$.

as a result of direct extension of the infection to areas immediately contiguous to abscesses. In a few instances, microscopic sections showed a purulent exudate within groups of alveoli scattered throughout an atelectatic lobe.

The well recognized fact that pulmonary suppuration is less common in active than in inactive animals is in accord with our hypothesis, as the more active rat is less likely to develop bronchial obstruction and subsequent atelectasis. The relative infrequency of pulmonary disease in active rats is in accord with experience in this and in other laboratories. Furthermore, this suggests that the infection can be prevented

by periodic administration of air mixtures rich in carbon dioxide. The hyperventilation of the lungs, resulting from such therapy, would probably prevent the accumulation of mucus in quantities sufficient to occlude a bronchus.

COMMENT

The interpretation of our observations is dependent on an understanding of the pathogenesis of atelectasis and the significance of this condition in relation to the development of pulmonary infection.



Fig. 5.—Obstructive atelectasis of the right lower lobe. The bronchus leading to this lobe is completely occluded by a plug of blood-stained mucus; $\times 2$.

Although the literature on this subject extends back into the first half of the nineteenth century, a widespread appreciation of the causative factors is recent and even now is not sufficiently understood. General interest in the subject has been aroused by numerous reports on the subject of "massive collapse of the lungs," and as a result of these studies the question is one of considerable clinical import. In addition to recent reports, this revival of interest in atelectasis has brought to light some remarkable observations by earlier investigators. The most notable of

these is probably that of Lichtheim⁹ who, in 1879, clearly demonstrated that the complete obstruction of a bronchus and subsequent absorption of air leads to collapse of the lung peripheral to the point of obstruction. In a recent report, Coryllos and Birnbaum¹⁰ made an exhaustive review of the literature and showed that there are two causes of collapse; the complete occlusion of a bronchus and compression of the lung. On the basis of this knowledge patients with postoperative massive collapse are being treated successfully by various procedures directed toward relief

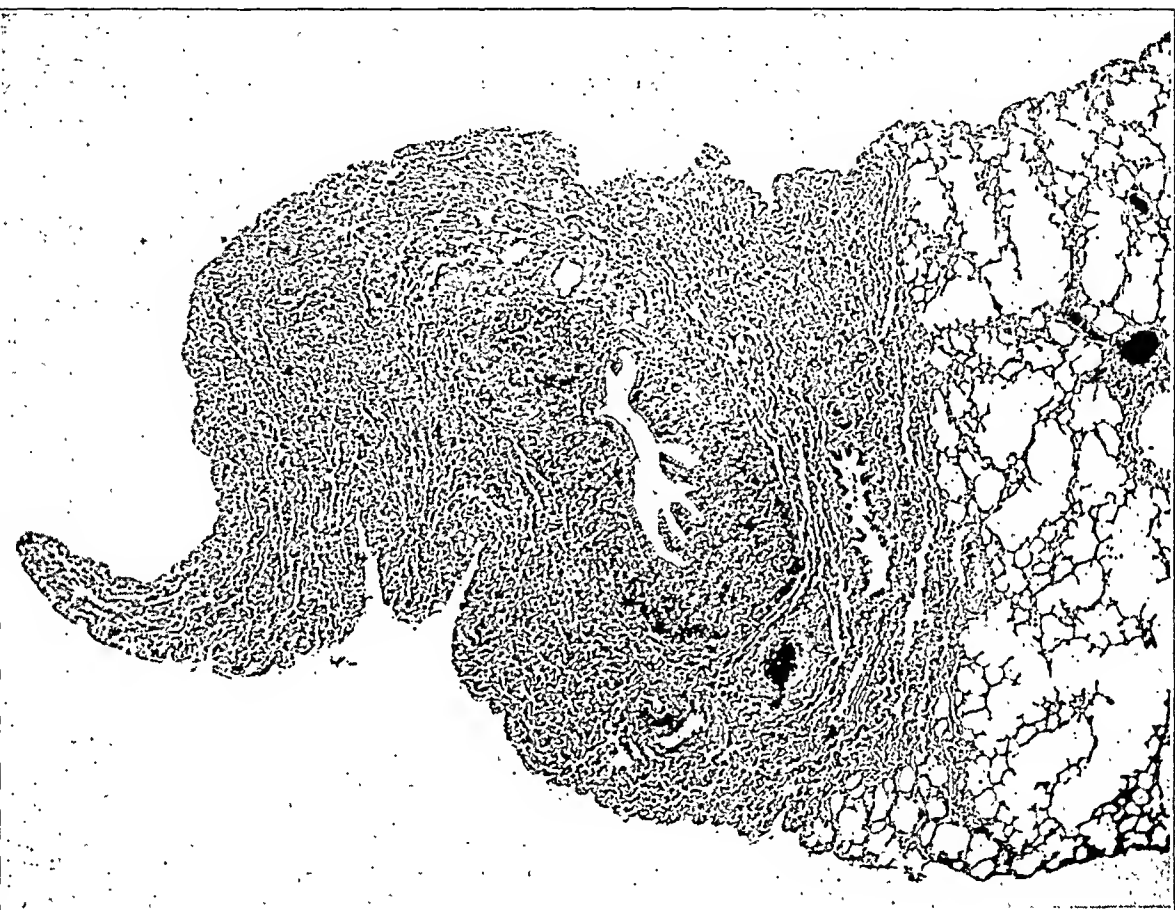


Fig. 6.—Obstructive atelectasis of the tip of the infracardiac lobe. There is no evidence of infection in either the collapsed or the normal portion of the section. Compare with figure 1.

of the obstructed bronchus. Coryllos and Birnbaum have presented additional evidence suggesting that lobar pneumonia may be the result of a similar phenomenon. Although the facts are not yet entirely clear, there is little doubt that obstructive collapse or atelectasis is an important factor in the development of certain pulmonary lesions in human beings.

⁹ Lichtheim, L.: Arch. f. exper. Path. u. Pharmacol. **10**:54, 1879.

¹⁰ Coryllos, P. N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, Arch. Surg. **16**:501 (Feb.) 1928.

In our own studies we have been particularly impressed with the frequency of the occurrence of atelectasis in white rats. This has been observed many times in animals apparently normal and showing no evidence of pulmonary suppuration. The areas of atelectasis have varied in size from the collapse of a minute portion at the tip of a lobe to a massive collapse of one entire side and the infracardiac lobe. In many instances there was no associated gross or microscopic evidence of infection. In others, smaller or larger abscesses were seen within the collapsed portions of the lungs. These observations lead us to the conclusion that atelectasis is a primary factor in the development of pulmonary infection in the white rat.

To substantiate this hypothesis it is necessary to show that obstructive atelectasis occurs in white rats showing no evidence of pulmonary infection and that organisms already present may cause abscesses in the collapsed lobes. On the latter point it is well known that obstruction to any part is an important factor in the localization of an infectious process. In many instances we have demonstrated occlusive mucous plugs in the bronchi leading to such collapsed lobes. The occurrence of excessive mucus in the bronchi of white rats has been frequently observed (Mitchell⁴ and Hektoen⁷). The points of occlusion have been demonstrated by injection of air and fluid into the trachea and by careful dissection of the bronchi leading to collapsed lobes. The objection that the occlusion may develop as the result of infection can be readily answered by our frequent observations of obstructive atelectasis in animals showing no evidence of pulmonary infection. In fact this is frequently found in animals apparently in perfect condition.

SUMMARY

Obstructive atelectasis is a common observation in otherwise healthy albino rats. The obstruction is frequently the result of the accumulation of mucus in the form of a plug completely occluding the bronchial lumen. Micro-organisms may be frequently obtained from the lungs of healthy animals (Jones²). On the basis of these observations, it is probable that the sequence of events in the pathogenesis of pulmonary disease in the white rat is the entrance of organisms into the lung, an obstructive atelectasis followed by the growth of organisms distal to the point of occlusion and the development of pulmonary suppuration. The established suppurative process may extend to other parts of the lung by a repetition of these changes or by direct extension to adjacent structures.

THE TREATMENT OF ACUTE EPIDEMIC POLIO-MYELITIS BY THE INTRATHECAL ADMINISTRATION OF EPHEDRINE *

M. BERNARD BRAHDY, M.D.

Assistant Attending Physician, Willard Parker Hospital

AND

I. H. SCHEFFER, M.D.

Resident Physician, Willard Parker Hospital

NEW YORK

Acute epidemic poliomyelitis is a systemic infection in which the most important lesions occur in the central nervous system. Unless the disease process is checked, the meningeal irritation is followed in a short time by manifestations of involvement of the nerve tissue proper. The initial toxic reaction in the cord or brain stem is a hyperemia and edema, resulting in a local increase in pressure. At the site of the local increase in pressure the smaller blood vessels are compressed, and the part of the cord supplied by these vessels becomes anemic. A deficient blood supply means a deficient oxygen supply. The injurious effects of anoxemia take place rapidly in the nerve tissue.¹ If the anoxemia is not relieved, injury to the nerve cells will result. In experimentally produced poliomyelitis in monkeys, Flexner and Lewis² found that "the chief lesion (in the cord) consisted of edema, injection of the vessels and punctiform and larger (pinhead) hemorrhages. The lesions tend to be most marked in regions of the spinal cord corresponding with the paralyzed groups of muscles. The congestion is more apparent than the hemorrhages." Peabody, Draper and Dochez,³ in their pathologic studies of human cases, found that "It is quite impossible to exclude the fact that the virus may exert some directly toxic action on these (nerve) cells, but in many ways, the clinical and anatomical pictures are readily explained by the pressure of the circulatory disturbance and of the exudate. . . . The damaging effects can be assumed to result in

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* From the services of Dr. Philip Moen Stimson and Dr. Henry W. Berg, Willard Parker Hospital.

1. Gomez, L., and Pike, F. H.: The Histological Changes in Nerve Cells Due to Total Temporary Anemia of the Central Nervous System, *J. Exper. Med.* **11**:257, 1909.

2. Flexner, S., and Lewis, P. A.: Experimental Epidemic Poliomyelitis in Monkeys, *J. Exper. Med.* **12**:236, 1910.

3. Peabody, F. W.; Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph of The Rockefeller Institute for Medical Research, IV, 1912.

part from the direct pressure on the nerve cells of hemorrhage, edema and exudate. There is also the additional factor of anemia following the constriction of the blood vessels by the same mechanism. On account of this pressure and anemia the nerve cells degenerate. If the hemorrhages and exudate are absorbed soon enough the cells may recover their function. If, on the other hand, the anemia and pressure have been prolonged or excessive, the nerve cells go on to complete necrosis. . . . It is noteworthy, however, that it is often extremely difficult to reconcile the clinical symptoms which are referable to pontine lesions with the actual autopsy findings. Cases which have bulbar paralysis during life may fail to show adequate anatomical lesions to account for death and other cases which have clinical evidence of spinal involvement may show changes only through the pons and medulla." Meltzer,⁴ commenting on these observations, stated that "It is possible that while the victim is still alive and the circulation active, hyperemia and edema are much more extensive than after the heart has stopped beating for a time."

In addition to the deleterious mechanical effect of the reaction in the central nervous system, some investigators⁵ feel that there is a direct toxic action on the nerve cells. Even if a direct toxic action does occur, it is important to maintain the resistance of the nerve cells at the highest level possible. The congestion and edema in the surrounding tissue which interfere with the nutrition and metabolism of the nerve cells are of great importance in the production of the paralyzes.

If the diagnosis of poliomyelitis is made in the preparalytic stage, we feel that the patient should be given convalescent serum. Shortly after the first paralysis appears, serotherapy fails to influence the course of the disease.⁶ At this stage, and later, treatment must be instituted to relieve the damaging local reaction in the central nervous system. To accomplish this, it is necessary to diminish the hyperemia and edema.

In the past, several methods have been tried, but without success. The injection of hypertonic solutions by vein or by rectum has been of uncertain value. Repeated lumbar puncture has not proved effective.⁷ In 1916, Meltzer⁴ tried epinephrine in a series of cases. The mortality

4. Meltzer, S. J.: *The Treatment of Acute Poliomyelitis*, New York M. J. **104**:337 (Aug. 16) 1916.

5. Howe, H. S.: *The Pathology of Human and Experimental Poliomyelitis*, J. Nerv. & Ment. Dis. **50**:409 (Nov.) 1919. Mönckeberg: *Anatomischer Befund eines Falles von Landry'schen Symptomkomplex*, München. med. Wchnschr. **45**:1958 (Nov. 10) 1903.

6. Mönckeberg: *The Epidemic of Poliomyelitis in New York in 1916*, Monograph of the Department of Health, New York City, 254, 1917. Aycock, W. L., and Amoss, H. L.: *The Serum Treatment of Experimental Poliomyelitis*, Bull. Johns Hopkins Hosp. **34**:361 (Nov.) 1923. Flexner, S., and Lewis, P. A.: *Epidemic Poliomyelitis*, J. A. M. A. **57**:1685 (Nov. 18) 1911.

7. Mönckeberg (footnote 6, first reference).

in his cases in which treatment was given was higher than in his control group.⁷ However, an important observation was made by Hoyne and Cepelka⁸ in cases in which epinephrine was given intrathecally. They noticed that in several instances the paralysis of a limb was temporarily lessened after treatment. In other words, the motor nerve cells regained their function temporarily as a result of the local astringent action of the epinephrine. This drug, however, is not suitable for the maintenance of a vasoconstrictor and astringent action. Its effects are rapid and intense, but of short duration. Moreover, a secondary vasodilatation sometimes occurs which may be harmful.

In 1924, Chien and Schmidt⁹ brought ephedrine to the attention of the medical profession. In contrast to epinephrine, ephedrine has a less intense and a more prolonged vasoconstrictor action and is not followed by a secondary vasodilatation.¹⁰ This makes it especially useful for local application in poliomyelitis.

The cases reported in this paper are those of patients with bulbar lesions admitted to the Willard Parker Hospital during August and September, 1928. As in other diseases, the percentage of very sick patients was higher in the hospital than in the city at large. On admission to the hospital, all patients were classified as severely ill or moderately ill. Moderately ill patients were those without prostration, whose bulbar lesions were of long standing without any evidence of extension. On admission some had nasal regurgitation and others, facial paralysis. In these cases, the prognosis for life was considered good. On the other hand, the majority of patients were very sick, were prostrated, had extensive bulbar involvement and gave the impression that their chances for recovery were small. These were classified as severely ill. We realize that without more numerous specific points on which to base a prognosis, such a classification may be fallacious. However, the patients we considered as moderately ill all survived, whereas among those considered severely ill the mortality was high, as will be shown later.

TECHNIC

Lumbar puncture was done on admission for diagnostic purposes in all cases. If the spinal fluid was under normal or slightly increased

8. Hoyne, A. L., and Cepelka, F. P.: Poliomyelitis, *J. A. M. A.* **67**:666 (Aug. 26) 1916.

9. Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine, *J. Pharmacol. & Exper. Therap.* **24**:339 (Dec.) 1924.

10. Rudolph, R. D., and Graham, J. D.: Notes on the Sulphate of Ephedrine, *Am. J. M. Sc.* **173**:399 (Jan.) 1927. Kreitmar, H.: Pharmakologische Wirkung des Ephedrins, *Arch. f. exper. Path. u. Pharmacol.* **120**:189, 1927. King, T., and Pak, C.: Ephedrine on the Nasal Mucous Membrane, *Chinese J. Physiol.* **1**:445 (Nov.) 1927.

pressure, from 4 to 6 cc. was removed for laboratory examination. If the pressure was greatly increased, spinal fluid was removed until the pressure was approximately normal. When ephedrine was administered, the last 2 to 4 cc. of spinal fluid was retained in the gravity tube. From 40 to 60 mg. of an ephedrine salt in 1 cc. of sterile water was added to spinal fluid and permitted to gravitate into the spinal canal. The average dilution was 50 mg. of drug in 5 cc. of fluid, or a concentration of about 1 per cent. In severe cases, it may be advisable to give two or more daily injections during the first few days.

Ephedrine was given intrathecally in ten cases during August and September. On admission, the patients in these cases were classified as severely ill with a poor prognosis for life. Five of the ten died, a mortality of 50 per cent. The first death occurred in the case of a young man who had a palatal paralysis of four days' duration. At the time of admission, he was apprehensive and restless; his temperature was 100.4 F., the pulse rate 110 and respirations, 22. There was involvement of the upper cervical nerves and the third, fourth, ninth and eleventh

*Bulbar and Bulbospinal Cases of Poliomyelitis in the Willard Parker Hospital
During August and September, 1928*

	Total No. of Patients	Moderate	Severe	Total No. of Deaths	Mortality, per Cent in Severe Cases
Untreated	19	7	12	9	75
Treated	10	0	10	5	50

cranial nerves. His condition grew rapidly worse, and he died twenty-four hours after admission. Another death was that of a boy, aged 8 years, who had a widespread bulbar and spinal involvement. Two injections of ephedrine were followed by an improvement, and no more was given. Five days later, the boy developed respiratory paralysis and died. In two other patients the drug was given in extremis; one died in one hour, the other in three hours. The failure of a therapeutic procedure under such conditions is not in itself an indication of inefficacy. Recovery or death is a definite but not the only criterion by which a therapeutic measure may be judged. It was our impression that in several instances improvement was more rapid in cases in which treatment was given than in the control cases.

CONTROL CASES

As a control group, we used all the other patients with bulbar poliomyelitis admitted to the hospital during August and September. On admission, the cases were classified as moderate or severe on the basis previously described. One patient admitted in September is not included because autopsy revealed a complicating bronchopneumonia. We did

not feel certain that death was due directly to poliomyelitis. There was a total of nineteen other cases in this group, seven moderate and twelve severe. Nine of the twelve patients with severe cases died, a mortality of 75 per cent, as compared with a mortality of 50 per cent among those treated with ephedrine. The criticism may be made that some of the bulbar cases in which treatment was not given were not included in the control group because they were classified as moderate. The accuracy of the classification has already been alluded to. However, we can take the total number of bulbar cases in which treatment was not given, including both moderate and severe, and compare the mortality percentage in the two groups. There was a total of nineteen moderate and severe cases in which treatment was not given, with nine deaths, a mortality of 47.4 per cent, which is little less than the mortality of 50 per cent in the severe cases, in which treatment was given, as shown in the accompanying table.

REPORT OF CASES

The following are abstracts of two cases in which ephedrine was used:

CASE 1.—H. L., a boy, aged $3\frac{1}{2}$ years, was admitted to the Willard Parker Hospital on Sept. 18, 1928. His present illness began seven days prior to admission with fever and malaise. Following this, there gradually developed a nasal tone to the voice, regurgitation of food through the nose and inability to swallow.

On physical examination, the child was extremely prostrated, well developed and well nourished. The pharynx filled up with saliva which the child seemed unable to swallow or expectorate. There was left facial paralysis, paralysis of the left half of the soft palate, deviation of the tongue to the left and marked weakness of the muscles of the neck and back. The patellar reflexes were greatly diminished. The heart and lungs were normal. The temperature was 102.4 F., the pulse rate 138, and respirations 38. The spinal fluid on admission was clear and under approximately normal pressure. There was a moderate mononuclear pleocytosis; the albumin, globulin and sugar content were normal. Forty milligrams of ephedrine was given intrathecally. There was no obvious reaction to the drug.

On September 19, the child was restless and irrational, and the general condition was poor. In addition to the condition found on admission, there were nystagmus and paralysis of the right half of the palate. The heart and lungs were normal. Frequent aspiration of the fluid accumulated in the pharynx was necessary. The patient regurgitated feedings given by mouth. The temperature was 102.4 F., the pulse rate 124, and the respiratory rate 30. Fluids were given rectally and intraperitoneally.

On September 20, the child was restless but less irrational, and the general condition was poor. The temperature was 102 F., the pulse rate 116, and respirations 30. Ten cubic centimeters of clear spinal fluid under slightly increased pressure was removed by lumbar puncture. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 21, the general condition was poor but was a little better than on the previous day. Nystagmus was no longer present. The muscles of the neck and back were stronger. The palatal, pharyngeal and facial paralyses

persisted. The patellar reflexes were stronger. The temperature was 101.2 F., the pulse rate 124, and respirations 28. Spinal fluid obtained by lumbar puncture was clear and under normal pressure. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 23, the patient was brighter. The temperature and pulse rate were normal. There was no change in the paralyses.

On September 24, the general condition was improved. The temperature and pulse rate were normal. The rectal and intraperitoneal administration of fluids was discontinued because the patient retained feedings by gavage.

On the 25th, the facial paralysis had diminished, but the palatal paralysis persisted. Gavage was still necessary.

On the 27th, the patient developed otitis media on the right side; the temperature was 102.8 F.

On the 29th, he was able to stand up unassisted. The palatal and pharyngeal paralyses persisted. There was a purulent discharge from the right ear.

On October 4, the patient was able to swallow, and gavage was discontinued. There was a slight discharge from the right ear. The temperature and pulse rate were normal.

On October 9, the general condition was good. The patient swallowed with greater ease.

On October 16, the patient was ready to be discharged but had developed impetigo contagiosa. On October 26, he was discharged. There were slight residual palatal and facial paralyses.

On November 14, a follow-up note stated that the child had been well since discharge. His general condition was good. There was no nasal regurgitation. Slight weakness of the facial and palatal muscles on the left side persisted. The other muscles were normal.

CASE 2.—P. C., a boy, aged 7 years, was admitted to the Willard Parker Hospital on Sept. 15, 1928. Two days prior to admission, he complained of headache and pain in the nape of the neck. The following day he vomited and developed difficulty in swallowing and nasal regurgitation.

On physical examination, the boy was fairly well developed, acutely ill and prostrated. There was slight rigidity of the neck, a lower left facial palsy, slight ptosis of the left upper eyelid, deviation of the tongue to the left and bilateral paralysis of the palate. Frothy secretion accumulated in the pharynx. There was a nasal tone to the voice and great difficulty in swallowing. The muscles of the neck and back were weak. The extremities, heart and lungs were normal. The temperature was 104 F., the pulse rate 136, and the respiratory rate 24. The spinal fluid obtained by lumbar puncture was under approximately normal pressure and contained 15 cells per cubic millimeter, 90 per cent of which were mononuclear. Forty milligrams of ephedrine hydrochloride was given intrathecally. There was no obvious reaction to the drug.

On September 16, the general condition was poor. The patient was restless and had developed incontinence of urine. The pharynx filled up rapidly with saliva. The temperature was 102.4 F., the pulse rate 138, and the respiratory rate 32. Forty milligrams of ephedrine hydrochloride was given intrathecally.

On September 17, the general condition was poor. The patient was irritable and was fed with difficulty. Gavage was discontinued, and fluids were given rectally and intraperitoneally. Forty milligrams of ephedrine hydrochloride was given intrathecally.

On September 18, the general condition was a little better. There was no spread of the paralysis; urine was voided normally. The temperature was 100.2 F. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 19, the condition was unchanged. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On September 20, 45 mg. of ephedrine sulphate was given intrathecally.

On Sept. 21, the general condition was better. The patient swallowed small quantities of fluids, but with great difficulty. There was a slight spasticity of the arms and legs. Forty-five milligrams of ephedrine sulphate was given intrathecally.

On the 22nd, the patient was able to swallow a little better. The extremities were normal.

On the 23rd, the general condition was much improved. There was still paralysis of the muscles of the left eyelid, face, tongue, both sides of the palate and the pharynx. The muscles of the neck and back were stronger. The temperature was normal.

On September 26, there was an improvement in speech. The patient swallowed more easily, occasionally regurgitating through the nose.

On October 7, the patient's general condition was good. His speech was greatly improved. He was able to hold up his head unassisted.

On October 11, he was discharged, much improved. There was residual weakness of the muscles of the left eyelid, the left side of the face and the left half of the palate. The muscles of the neck and back were normal, except the left sternocleidomastoid which was a little weak. The extremities were normal.

On November 11, a follow-up note stated that the patient experienced a little difficulty in swallowing for a time after discharge, but there was no regurgitation. There was a nasal tone to the voice. His general condition was good. The residual muscle weaknesses are the same as at the time of discharge.

COMMENT

In poliomyelitis, injurious hyperemia and edema in the cord and brain stem occur. A local increase in pressure and an anoxemia result, which impair the function and injure the nerve cells. The rapid relief of this local reaction is of paramount importance. The direct application of ephedrine to the lesion by intrathecal administration seems, therefore, a rational method of treatment.

In a disease with as varied a course as has poliomyelitis, the evaluation of a therapeutic measure is difficult. In our small series including only bulbar cases in which the prognosis for life was poor, the mortality was 50 per cent. In a control group of patients with apparently similar cases admitted to the hospital during the same time interval, the mortality was 75 per cent.

We feel that our patients were benefited and the mortality reduced by the use of ephedrine. In interepidemic years, the material available in one hospital is small. For this reason, we present our first series of cases as a preliminary report so that the treatment with ephedrine may be tried in other hospitals.

THE EFFECT OF HYPNOSIS ON BASAL METABOLISM *

JACOB GOLDWYN, M.D.

Senior Assistant Physician, Worcester State Hospital
WORCESTER, MASS.

In the past, work has been done concerning the effect of mental activity on basal metabolism. Some investigators, Speck,¹ Loewy,² Johansson³ and Benedict and Carpenter,⁴ found a slight increase in the metabolic rate during mental activity. Grafe,⁵ in his monograph, also concluded that mental effort probably has an influence on metabolism.

The effects of strong emotional reactions on basal metabolism in the waking and in the hypnotic states have also been studied. Grafe⁶ mentioned a metabolism experiment in which intense sorrow increased the metabolic rate. Du Bois⁷ cited a similar observation brought on by anger. Like observations have been made by Hafkesbring and Collett,⁸ who noticed that harsh or sudden noises had a tendency to increase metabolism. Landis⁹ noted that strong emotions usually cause an increase in the metabolic rate. In his experiments, anticipation of a strong electrical stimulation raised the metabolism in the three persons tested, 6, 17 and 37 per cent.

In making tests on psychasthenic war veterans, Ziegler and Levine¹⁰ found a marked rise in metabolism in eleven cases; in three, there was

* Submitted for publication, July 10, 1929.

* From the Psychiatric Service of the Worcester State Hospital.

1. Speck: Untersuchungen über die Beziehungen der geistigen Thätigkeit zum Stoffwechsel, Arch. f. exper. Path. u. Pharmakol. **15**:81, 1882.

2. Loewy: Ueber den Einfluss einiger Schlafmittel auf die Erregbarkeit des Athemcentrums nebst Beobachtungen über die Intensität des Gaswechsels im Schläfe beim menschen, Berl. klin. Wchnschr. **28**:434, 1891.

3. Johansson, J. E.: Ueber die Tagesschwankungen des Stoffwechsels und der Körpertemperatur in nüchternen zustande und vollständiger Muskelruhe, Skandin. Arch. f. Physiol. **8**:105, 1898.

4. Benedict and Carpenter: United States Department of Agriculture Office of Experiment Stations, 1909, Bull. 208.

5. Grafe, E.: Ergebn. d. Physiol. **21**:499 (part II) 1923; Klin. Wchnschr. **2**:1005, 1923.

6. Grafe and Traumann: Zur frage des Einfluss psychischer Depressionen und der Vorstellung schwerer Muskularbeit auf den Stoffwechsel (Untersuchungen in der Hypnose), Ztschr. f. d. ges. Neurol. u. Psychiat. **62**:237, 1920.

7. Du Bois: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927, p. 411.

8. Hafkesbring, R., and Collett, M. E.: Day to Day Variations in Basal Metabolism of Women, Am. J. Physiol. **70**:73, 1924.

9. Landis, C.: Studies on Emotional Reactions: IV. Metabolic Rate, Am. J. Physiol. **74**:188, 1925.

10. Ziegler, L. H., and Levine, B. S.: The Influence of Emotional Reactions on Basal Metabolism, Am. J. M. Sc. **169**:68, 1925.

a fall, and in one, no change. They produced emotional situations by having the veterans, during the breathing period, think of their disagreeable war experiences.

Comparatively speaking, little work has been done concerning the effect of strong emotions, suggested by means of hypnosis, on basal metabolism. In all probability, Grafe has done more work in this field than any one else. In 1920, he and Traumann⁶ studied two subjects under hypnosis. One subject, under the hypnotic suggestion of depression, showed an increase of from 6 to 12 per cent in the metabolic rate, while the other manifested no appreciable change. Later, Grafe and Mayer¹¹ experimented on ten more subjects. The basal metabolism of each subject was determined under deep hypnosis, and then various emotional stimuli were given each subject while under hypnosis. The basal metabolism was determined under these conditions. Dreadful calamities, such as the amputation of arms, death of relatives and fights with cannibals, were suggested. In six subjects a distinct rise ranging from 8 to 25 per cent was found; in one case, only a slight rise, and in another, no change. Two subjects received pleasant suggestions; here only a slight rise in the metabolic rate was noted.

Grafe concluded that emotions may cause a distinct increase in metabolism and that emotions which produce sorrow increase the metabolism more than the ones that cause joy.

As far as I can discover, there has been no attempt, at least on a large scale, to determine what effect hypnosis, per se, has on basal metabolism. In this work the purpose was to obtain, by hypnosis, as complete a mental and physical relaxation as possible and then determine what effect, if any, this condition had on basal metabolism. Instead of stimulating mental activity, as did other investigators, suggestions were given to produce as complete a mental passivity as could be brought about.

Eighteen young normal men and women—mostly students of nursing and occupational therapy—volunteered for this work. None of them presented any gross physical or mental abnormalities.

METHODS

The procedure varied in different cases. In some, the subjects were first placed under hypnosis. Only those who went under deeply and who experienced no subjective mental or physical discomfort were selected to continue with the experiment. A test of the basal metabolism was made on each in the waking state under the usual conditions. Readings of the blood pressure, pulse rate and respiration were made. Blood was taken for a complete blood count and chemical analysis. That day, or a few days later, and in exceptional cases several days later, the same

11. Grafe, E., and Mayer, L.: Ueber den Einfluss der Affekte auf den Gesamtstoffwechsel, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **86**:247, 1923.

procedure was repeated, only this time under deep hypnosis. Suggestions to induce as complete a mental and physical relaxation as possible were repeatedly given under hypnosis, before the actual taking of the basal metabolism. It was noticed that whenever suggestions were made repeatedly, even during the breathing period of the basal metabolism procedure, there was a tendency for the basal metabolic rates to be

TABLE 1.—*Basal Metabolism, Pulse, Respiration and Blood Pressure Readings in the Waking State and Under Hypnosis**

Case	Age	Sex	State	Basal Metabolism, per Cent	Pulse Rate	Respira- tions	Blood Pressure
1	19	M	W	+ 6.5	75	15	110/76
			H	— 1.8	67	9	98/50
2	20	M	W	+ 2.5	62	12	92/48
			H	— 1.5	62	13	96/66
3	22	F	W	— 0.5	60	16	110/80
			H	— 2.5	66	16	104/74
4	22	F	W	— 4.0	70	14	104/64
			H	—11.0	60	15	100/74
5	21	F	W	— 4.7	64	16	104/60
			H	— 9.0	62	14	110/74
6	19	M	W	— 5.3	52	14	98/50
			H	—10.3	52	16	106/68
7	22	F	W	— 6.5	64	12	92/54
			H	— 9.5	62	11	92/54
8	24	M	W	— 7.0	66	14	108/72
			H	— 9.4	70	9	100/52
9	34	F	W	— 8.1	60	16	102/68
			H	— 8.7	62	12	102/74
10	22	F	W	— 8.1	64	18	110/68
			H	— 9.0	66	12	104/68
11	26	F	W	— 8.5	68	20	108/64
			H	—14.4	64	20	100/72
12	20	F	W	— 9.2	88	16	104/78
			H	—14.0	80	15	108/72
13	22	F	W	—10.3	64	15	108/58
			H	—11.7	54	15	94/64
14	20	F	W	—11.9	66	12	102/68
			H	—13.0	60	8	110/88
15	20	F	W	—12.8	76	14	96/64
			H	—16.1	78	12	112/80
16	20	F	W	—14.0	60	14	90/36
			H	—21.0	62	14	98/68
17	20	F	W	—14.5	70	15	106/66
			H	—20.0	72	12	104/60
18	25	F	W	—15.5	68	20	94/50
			H	—19.0	64	12	94/38

* The physical observations, the temperature and the urinalyses were all essentially normal. The readings under pulse and respiration are the average.

W indicates the waking state; H, the hypnotic state.

higher than the ones in which the suggestions were given only at the start of the experiment.

In other cases, the procedure varied in that the subject had the normal basal metabolic rate taken before any attempts were made to see whether or not he was a good hypnotic subject. Later the basal metabolism was done with the subject under hypnosis.

In a few cases, the basal metabolic rates were taken first with the subjects under hypnosis and then with them in the waking state.

It was observed that the variation in the order of procedure had no appreciable effect on the results.

Whenever a subject did not attain to an apparently complete mental and physical passivity under hypnosis, the tests were repeated. All tests

TABLE 2.—*Blood Chemistry and Blood Count Readings as Found in the Waking State and Under Hypnosis**

Caso	State	Nonprotein Nitrogen	Urea	Uric Acid	Sugar	Creatinine	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Polymorpho-nuclears, per Cent	Lymphocytes	Eosinophils	Transitionals	Basophils
1	W	31	20	3.4	100	1.1	80	460	660	56	40	2	2	0
	H	33	14	2.9	80	1.7	80	400	670	54	42	1	1	0
2	W	29	12	3.8	111	1.5	90	465	740	56	41	2	1	0
	H	37	14	4.4	83	1.5	85	400	645	59	38	1	2	0
3	W	27	12	3.2	100	1.4	80	394	1,375	63	33	1	0	0
	H	27	11	2.9	93	1.4	80	388	1,240	67	32	0	1	0
4	W	31	15	4.3	83	1.4	80	492	795	47	52	1	0	0
	H	80	460	790	83	16	1	0	0
5	W	26.5	11	4.3	114	1.5	80	465	750	58	39	1	1	1
	H	80	460	755	61	37	1	0	1
6	W	32	16	4.5	105	1.5	95	395	1,000	69	31	0	0	0
	H	38	18	4.4	105	1.5	95	487	490	48	50	0	2	0
7	W	31	14	3.3	93	1.4	85	433	700	64	34	1	1	0
	H	30	13.4	3.2	91	1.4	85	443	915	69	27	0	3	1
8	W	30	12	3.1	104	1.3	80	490	830	53	43	2	2	1
	H	29	12	3.9	100	..	85	497	805	56	44	0	0	0
9	W	38	14	2.3	93	1.3	80	415	655	73	23	0	4	0
	H	34	11	2.3	111	1.1	80	408	675	65	33	0	2	0
10	W	30	13	4.7	125	1.4	80	512	785	49	48	0	3	0
	H	36	20	4.0	121	..	95	475	990	63	33	0	1	0
11	W	35	14	3.3	105	1.8	80	424	495	65	35	0	0	0
	H	32	13.4	3.4	100	1.6	85	390	655	46	51	1	1	1
12	W	25	11	3.4	117	1.1	85	497	1,035	63	33	2	1	1
	H	25	11	3.5	113	1.1	80	490	625	73	26	1	0	0
13	W	38	15	3.6	108	1.2	80	520	960	77	20	0	3	0
	H	37	12	3.4	107	1.1	80	480	430	33	64	1	0	2
14	W	26	13	4.4	83	1.1	85	434	590	50	50	0	0	0
	H	24	19	4.4	123	1.1	80	469	590	48	49	1	0	1
15	W	32	12	2.4	91	1.4	80	478	810	59	37	0	3	0
	H	25	12	2.4	100	1.4	85	532	795	70	25	3	2	0
16	W	37	19	3.2	83	1.4	85	492	825	55	41	1	3	0
	H	40	16	3.8	100	1.1	85	425	615	56	41	2	2	0
17	W	29	15	2.9	105	1.7	85	408	665	59	37	0	4	0
	H	37	15	3.1	103	1.4	85	408	720	67	33	0	0	0
18	W	33	15	2.7	87	1.7	80	462	845	57	39	2	2	0
	H	32	14	3.1	83	1.6	80	494	830	72	27	0	1	0

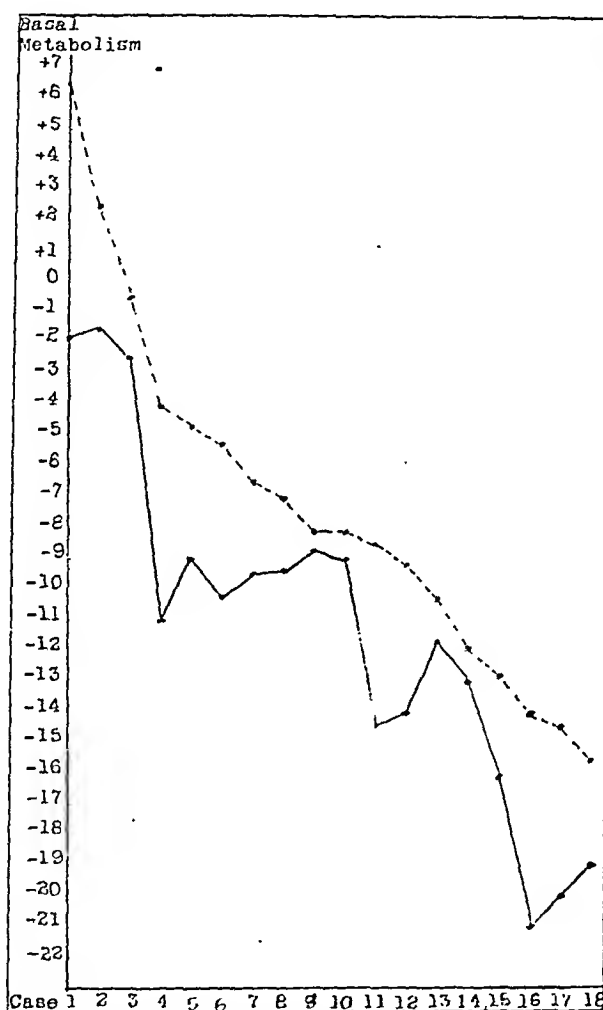
* For true reading under red blood count, multiply the figure given by 10,000. To obtain the correct white blood cells, multiply by 10.

in which the subject reported more than minimum mental activity were disregarded.

The basal metabolic readings were obtained by the use of a Benedict closed circuit apparatus. The results were calculated according to the Harris-Benedict and the Aub-Du Bois standards, and the means of the two values were taken.

Tables 1 and 2 contain the results of the observations. In the first table are given the readings of the basal metabolism, pulse, respiration

and blood pressure as determined in the waking state and under hypnosis. From this it can be seen that the outstanding observations are those with the subject under hypnosis. Under hypnosis, not one case resulted in an increase of basal metabolism. All showed decreases ranging from 0.6 to 8.3 per cent, with an average decrease of 3.88 per cent. It will also be noted that in the majority of cases the pulse and respiration readings tended to be lower with the subjects under hypnosis than in the waking state.



The relation of the normal basal metabolism to that under hypnosis. The broken curve indicates the waking state; the solid curve, the hypnotic state.

The observations on blood pressure gave no constant changes.

As seen in table 2, the blood count and chemical analysis presented no characteristic variations with the subjects under hypnosis.

The accompanying chart gives a clear picture of the relationship of the normal basal metabolism to that with the subject under hypnosis.

COMMENT

A person may be under hypnosis without attaining mental and physical passivity—stray thoughts may pass through the mind, fear may

produce some disturbance or the body may be in an awkward position causing discomfort. But under proper hypnotic suggestions both mental and physical activities can be brought to a decidedly low working level. A basal metabolic rate taken under such conditions is representative of the metabolism of the body at a low degree of function.

The question arises as to the significance of an average decrease of 3.88 per cent in the basal metabolism under hypnosis. It is realized that such a drop in itself is of no importance, but when it appears consistently in every case it becomes of definite significance.

SUMMARY

The basal metabolism, pulse, respiration, blood count and chemical analysis of the blood of eighteen normal subjects were studied both in the waking state and in the hypnotic state.

In every case it was found that the basal metabolism was decreased under hypnotic suggestions tending to produce mental and physical inactivity. The decreases varied from 0.6 to 8.3 per cent, with an average decrease of 3.88 per cent.

There was a tendency for the pulse and respiration to be lower under hypnosis.

The blood pressure, blood count and chemical analysis of the blood showed no constant change under hypnosis.

CONCLUSIONS

Hypnotic suggestions tending to produce mental and physical inactivity decrease normal basal metabolism.

THE EFFECT OF LESSENERED RESPIRATORY RESERVE ON THE BLOOD AND ON THE CIRCULATION

AN EXPERIMENTAL STUDY *

WILLIS S. LEMON, M.D.

ROCHESTER, MINN..

The experimental study of respiratory reserve reported here is a continuation of similar work done a year ago. At that time, the efficiency of the mechanical factors of respiration received most attention. This study deals more particularly with the effects produced on the respiratory reserve by lessened mechanical efficiency. It represents an attempt to discover the point at which reserve is lost, at which respiration as a function is inadequate, and at which circulatory aid is required so that the animal can maintain a comfortable existence.

From among the group of animals under observation, an especially intelligent dog was chosen and was taught to lie quietly while wearing the usual mask employed in taking basal metabolic readings. This training was necessary before the undertaking of any of the operations that were employed and that were designed to lessen mechanical efficiency and to decrease vital capacity. The dog was vigorous and healthy in all respects, and was found to be organically healthy on careful general examination. Ether anesthesia was used in all operations, and strict surgical technic was employed.

OBSERVATIONS

First Period.—Operations.—On March 22, 1927, an attempt was made to section and perform evulsion of all the intercostal nerves on the left side. The first nerve was difficult to reach because of its normal inaccessibility. There is some doubt whether evulsion of it was effected. Portions of the lower eleven nerves were removed.

On March 31, a similar operation was done on the right side. Portions of the lower eight intercostal nerves were removed. The nerves were cut as near as possible to their spinal origins so that a large fraction of the intercostal muscles might be rendered functionless.

On April 7, with the use of the usual technic employed in phrenic neurectomy, evulsion of the right phrenic nerve was effected through an incision in the neck. With the same method of examination that was used in a former study, it was apparent that the right leaf of the diaphragm was totally paralyzed.

* Submitted for publication, June 1, 1929.

* From the Division of Medicine, the Mayo Clinic.

* Read before the American Society of Clinical Investigation, Atlantic City, N. J., April 29, 1929.

* Work done in the Division of Experimental Surgery and Pathology, the Mayo Foundation.

On April 12, exeresis of the phrenic nerve was done on the left side.

Comment.—The muscular equipment on which respiratory competence depends was now limited to the muscles attached to the ribs on the vertebral side of the operative sites and to the extrarespiratory muscles about the neck and shoulders that are used by normal dogs only following severe muscular exertion. The respiratory function of the diaphragm was excluded; its effect on intra-abdominal pressure changes was removed; only its function as a partition separating the body cavity into two large portions remained.

The behavior of the dog was similar in all respects to that of the members of the large group formerly observed. It lived comfortably, played about like its normal mates, and on casual examination could not be distinguished from them. It could not, however, respond to vigorous exercise with the same ease because its vital capacity was lessened. The effect of the operative procedures on the dog was precisely like that of the former group and can be described by quoting the observations made on them as a whole:

"When the nerves are sectioned on only one side, there is immediate or delayed temporary or persisting asymmetry in the chest with a definite and measurable loss in the outward movement of the costal arch and margin during inspiration. When one-half of the diaphragm is paralyzed, the costal arch and margin do not increase their outward movement during inspiration either in man or dog. When the intercostal muscles on one side are paralyzed, the costal arch and margin continue to move away from the middle line even though the diaphragm is normal. These observations hold true whether they are made during the examination of experimental animals or of man following surgical procedure, accidents or disease. Moreover, the section of all the intercostal nerves on one side or on both sides, combined in whatever order possible with evulsion of one phrenic nerve or both phrenic nerves still leaves an animal capable of ordinary activities and with the ability to develop a vital capacity in excess of tidal air requirements. The introduction of phrenic neurectomy does not alter in any way the movement of the chest wall. Asymmetry and reduction of outward lateral movement occur when the intercostal nerves on one side are sectioned. The reduction amounts to from 30 to 50 per cent of normal depending on the number sectioned, and the movement of the chest wall is accomplished by muscles incapable of motion against the same resistance that would be overcome by normal muscles. Symmetry and bilateral reduction in movement result from bilateral section of the intercostal nerves. Regardless of the order in which the phrenic nerve paralysis is introduced, these movements remain the same.

"Vital capacity becomes progressively diminished and proportionately with the increase in muscular dysfunction produced by the several combined operations. When all the intercostal nerves are sectioned and both phrenic nerves cut, the animal cannot be anesthetized with ether without caution nor can he breathe comfortably through a spirometer while he is wearing the required mask. Vital capacity then is reduced almost to tidal air requirements."

These tests, however, had to deal with observations on functional behavior, and the consequences of operative intervention were expressed only in alterations of anteroposterior and transverse diameters during respiratory movements. Experiments designed to indicate alterations in volume were considered but were not technically simple enough to exclude a large percentage of error. It was decided to measure the intake of air for each unit of time following each operation and to compare the results with those obtained before starting any of the operative procedures, with the belief that the result would be the equivalent in value to alterations in volume. The data in table 1 represent the measurements after

each operation; those of the same dog before operation may serve as a control. The accompanying illustration is a tracing of respiratory movements, showing that the dog was lying quietly and breathing in a tranquil manner. Readings were not accepted unless this type of tracing accompanied them.

The dog was returned to the kennels and allowed to live under normal surroundings for a year. It was examined from time to time, but remarkable changes did not occur. Its general health improved; it became more playful than before the operations were done, and it gained in weight. Difficulty was not experienced either in urination or in defecation despite paralysis of the whole diaphragm and of the upper abdominal muscles. The muscles of the lower portion of the abdomen seemed to undergo hypertrophy; the abdominal wall was always rigid when examined. In other respects, the dog was bilaterally symmetrical; its respiratory movements were normal, and it was dyspneic only after unusual exertion. It could run up and down stairs without embarrassment.

TABLE 1.—*Effect of Operations on Vital Functions of a Dog **

Dog 1	Weight, Kg.	Pulse Rate	Respiration Rate	Ventilation, Liters Each Minute
Normal	15.0	72	9	3.12
	95	14	3.65
	93	12	3.32
	65	14	2.64
Intercostal nerves cut on left side.....	14.6	86	13	3.18
	79	11	2.76
	77	11	2.72
	81	13	3.05
Intercostal nerves cut on right side.....	14.0	97	15	3.62
	89	15	3.75
	83	14	3.95
	101	16	3.91
Phrenic nerve cut on right side.....	13.3	73	11	2.02
	71	10	2.52
	66	10	2.48
	71	10	2.49
Phrenic nerve cut on left side.....	13.2	64	16	3.34
	78	16	2.94
	70	15	3.04
	75	16	3.35

* The figures indicate that the respiratory function was adequate to supply sufficient ventilation under all conditions and that the vital capacity provided for a normal amount of tidal air.

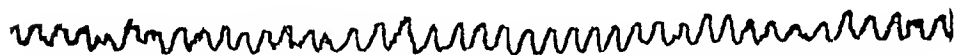
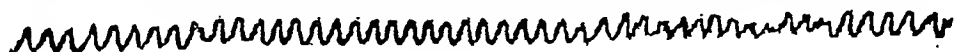
Second Period.—Operation.—On April 12, 1928, a year following the last previous operation, the abdominal cavity was opened and the diaphragm was resected from its ventral attachment. A single portion approximately 6 cm. in diameter and cut so that it involved both leaves was removed from the diaphragm. It was noted that the whole diaphragm had taken a position high in the thorax and that atrophy was so excessive that the usual color of the diaphragmatic muscle had faded to a light pink; the muscular portion could be distinguished from the tendinous portion only with difficulty, and the whole diaphragm had become so thinned that the lungs were plainly visible through it.

Comment.—The description of the operation just given is approximately in the words of the surgeon who operated. The condition described is exactly the same as that which I described in my earliest work on phrenic neurectomy. In the animal described in this paper, after paralysis of a year's duration, there was no suggestion of regeneration in any part of the diaphragm from the center to the periphery. The microscopic appearance was similar to that previously described and the vascularity of the musculature had the appearance of that of a normal diaphragm.

After a stormy convalescence in which dyspnea was the predominating symptom, the dog finally recovered and again lived a normal life. It learned to breathe differently, however. The chest was raised almost as one piece during inspiration and at the same time the lower part of the abdomen contracted strongly. This paradoxical abdominal movement suggested that perhaps the abdominal muscles were compensating for the loss of a competent diaphragmatic partition and were contracting during inspiration so that the abdominal contents might be retained within the abdomen and excluded from the thoracic cavity, thus preventing undue embarrassment or real respiratory incompetence.

It should be remembered that the dog is a pronograde animal of carnivorous habit, and the abdominal cavity has a relatively small visceral content. One could not predict the response of orthograde animals to similar treatment.

Moreover, the possibility of regeneration of intercostal nerves had to be kept constantly in mind. In other animals, however, in which evulsion of intercostal nerves had been performed, such regeneration had not been found at necropsy. From analogy, therefore, it was considered that an animal was now being studied in which, undisturbed, were five complete sets of intercostal muscles, vertebral muscles and the posterior portion of nineteen intercostal muscles as well as the accessory groups. Also, the lower portion of the abdominal muscles were acting



Kymograph record of respiration showing quiet breathing.

normally. The three functions of the diaphragm, respiratory, pressure-producing, and partition-effecting, were almost completely destroyed.

The dog was again allowed to live in the kennels and behaved as its normal mates.

Seven months later or twenty months from the date of the first operation, studies of the blood were made to determine whether or not the long continued reduction in vital capacity could have brought about erythrocytosis, change in blood volume, in the hematocrit volume, in the hemoglobin content, in the arterial and venous oxygen content or alterations in the blood count itself.

Readings of the intake of air for each unit of time were again made and were of the same character as those reported in table 1. The weight was 15.2 Kg. The surface temperature was 36.3 C. On the first test, the pulse rate was 66, the respiratory rate, 20, and the ventilation, in liters, each minute, was 3.96. On the second test, the corresponding figures were, respectively, 88, 18 and 4.56. From Nov. 14, 1928, to March 16, 1929, blood counts were recorded (table 2).

The hematocrit values were taken at various times from Nov. 16, 1928, to March 16, 1929. The values for erythrocytes were from 42 to 45 per cent, and for plasma from 55 to 58 per cent, which represent normal proportions.

Numerous tests of blood volume were made in the interval between November, 1928, and February, 1929, and a normal dog of equal weight and breeding was

used as a control. The volume estimations varied slightly but were always within normal limits. The last test on February 21 gave readings that were exactly the same for the control animal and for the test animal. Both dogs had 86 cc. of blood for each kilogram of body weight.

On Dec. 12, 1928, the readings for oxygen in per cent by volume were as follows: arterial oxygen content, 19.7 per cent, and venous oxygen content, 12.8 per cent. Oxygen capacity was 22.6; oxygen saturation was 87 per cent. The amount of hemoglobin was 16.9 Gm. in each hundred cubic centimeters of blood.

On Jan. 14, 1929, an electrocardiogram was taken, although abnormality of the heart had not appeared and its size had remained stationary. Roentgenographic examinations had been used to confirm general examinations. It was expected that the electrocardiographic reading would be normal, although the possibility of right ventricular preponderance was kept in mind. Yet any significant preponderance could hardly be expected in an animal the lungs and heart of which were equally unaffected organically. The electrocardiographic report was as follows: inversion of T wave in all three leads; sinus arrhythmia; sino-

TABLE 2.—*Blood Counts and Hematocrit Values on Various Dates After Operations*

Date	Hemo- globin, Per Cent (Sahli)	Erythro- cytes, Millions	Leukocytes, Thou- sands	Lympho- cytes	Differential Count, Per Cent *				Cells by Hem- atocrit, Per Cent
					Large Mono- nuclear Leuko- cytes	Transi- tionals	Neutro- phils	Eosin- ophils	
11/14/28	120	7.43	5.7	14	2	2	78	4
11/16/28	45
12/ 3/28	115	5.86	9.3	18	4	2	72	4
12/27/28	120	6.07	9.7	15	1	6	78	..	42
1/15/29	130	6.71	5.0	8	..	15	69	8	45
2/18/29	43.3
2/21/29	95	6.25	5.6	22	74	2
2/27/29	95	6.38	9.2
3/ 8/29	85	4.91	15.7
3/16/29	90	5.76	12.4	42

* 200 cells were counted on each date.

auricular block; slight slurring of the Q R S wave in all three leads, and slight right ventricular preponderance. This is essentially normal for a dog and does not indicate that the respiratory reserve had been reduced to such a degree of decompensation as to require unusual cardiac cooperation.

All tests of circulation and of the blood itself confirm the belief that this dog still retained sufficient respiratory reserve so that it did not require assistance from the circulation to maintain its competence under ordinary living conditions. The readings were taken after a long interval of time to avoid alterations, such as compensatory erythrocytosis, that might have been anticipated at an earlier date and in which I was not especially interested.

Third Period.—Operation.—On Feb. 28, 1929, the dog's abdominal cavity was again opened. Roentgenographic examinations had shown that the stomach had migrated into the pleural space. When adhesions had been broken down, it was discovered that the whole stomach, a part of the duodenum, and all but two of the lobes of the liver had forced their way into the thorax. That part of the diaphragm remaining presented the appearance elsewhere described. It was thin, translucent and flapped back and forth with respiratory movements. It was caught with forceps, drawn downward and an incision was made parallel to the costal attachment, the diaphragm being detached from side to side and backward

as far as possible. The strip of diaphragm between the line of incision and the aperture originally made was not removed.

Comment.—After recovery from the anesthetic, the dog ran about the recovery room seemingly unembarrassed in its breathing. The dog's recovery has been quite uneventful, but the animal has been kept at rest. The regimen of rest has been imposed so that healing might not be interfered with, but more so that compensation might be developed and unnecessary strain might not be put on the function of respiration. Examination of the blood on March 8 and 16 gave the following results, respectively: hemoglobin, 85 and 90 per cent; erythrocytes, 4,910,000 and 5,760,000, and leukocytes, 15,900 and 12,400 in each cubic millimeter. The differential count of the leukocytes showed them to be present in normal proportions. The per cent by volume of the erythrocytes was relatively normal, according to the hematocrit reading.

The volume of air breathed each minute was again measured and was found to be somewhat larger than that previously recorded. Three estimations each were made of pulse rate, respiratory rate and ventilation in liters each minute. The results were as follows: pulse rate, 76, 82 and 80; respiratory rate, 22, 22, and 22, and ventilation in liters each minute, 4.64, 4.75 and 4.31. Surface temperature and air temperature also were taken three times, in degrees centigrade, with the following results: surface temperature, 36.4, 37.6 and 37.2; air temperature, 21.4, 27.0 and 24.0.

On March 20, 1929, the dog was healthy and active, and did not show evidence of respiratory embarrassment. The lowered percentage of hemoglobin, a reduced erythrocyte count and an attendant rise in the number of leukocytes were the only alterations that had appeared since the last operation. The ventilation each minute has increased but has reached only high normal values.

SUMMARY AND CONCLUSIONS

In this study of the respiratory reserve, the muscles ordinarily responsible for the production of inspiration and expiration have been rendered functionless in whole or in part by evulsion of their motor nerve trunks. All of the several functions of the diaphragm have been interfered with so that a state characteristic of a mammal has been changed, and the final state is one that, in respect to the diaphragm, virtually is characteristic more of birds than of mammals.

Vital capacity has been lessened but never beyond the point where it failed to be equivalent to tidal air. The ventilation in liters of air breathed each minute reached a high normal amount but was not distinctly abnormal at any time.

The hemoglobin decreased from high to low normal percentages, but the amount of hemoglobin for each hundred cc. of blood was within normal limits.

The hematocrit percentages varied slightly but were never abnormal.

The arterial and the venous oxygen content and the oxygen of the blood were essentially normal. However, oxygen saturation of both arterial and venous blood was lowered. The number of erythrocytes failed to indicate either temporary or permanent erythrocytosis such as might have been anticipated had respiratory competence been destroyed.

The heart has remained normal functionally, has not shown evidence of hypertrophy, and the electrocardiogram cannot be interpreted as evidence to indicate any definite failure of the right ventricle.

The experiment illustrates the degree to which muscular dysfunction may be carried before respiratory incompetence develops in an animal which has a normal heart and normal lungs. It seems to confirm the independence of two fundamental functions having interrelated duties; great loss of reserve in one is required before demonstrable evidence of cooperative support is provided by the other.

EXOPHTHALMIC GOITER

THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID *

WILLARD OWEN THOMPSON, M.D.

Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School

AND

BERNICE ALEXANDER, A.B.

BOSTON

One of us (W.O.T.) has previously shown that the concentration of protein in cerebrospinal fluid is high in most cases of myxedema, and usually drops to within normal limits following the administration of desiccated thyroid.¹ Similar measurements² have now been made in several cases of exophthalmic goiter before any treatment was started and after the body weight had reached a stationary level following a subtotal thyroidectomy. The observations are the opposite of those in myxedema. Before treatment, the concentration of protein is usually within the lower limits of normal.³ It shows a well marked increase (eleven out of fifteen cases) in association with a gain in body weight and a reduction in basal metabolism after operation. This is illustrated in fifteen unselected cases in the accompanying table and illustration. It may be noted that, as usual, there are wide individual variations in protein concentration. Our experience has been, however, that at least in patients with myxedema, the concentration is relatively constant in each case during a stationary state.

In one patient whose thyroid gland was apparently functioning normally, we were able to observe the effect of the administration of thyroid on the concentration of protein in spinal fluid. A well marked increase in basal metabolism during its administration was associated with a well marked decrease in the concentration of protein.

* Submitted for publication, May 24, 1929.

* From the Metabolism and Neurological Laboratories of the Massachusetts General Hospital.

1. Thompson, W. O.; Thompson, P. K.; Silveus, E., and Dailey, M. E.: The Protein Content of the Cerebrospinal Fluid in Myxedema, *J. Clin. Investigation* 6:251, 1928.

2. The method of Denis and Ayer (Method for Quantitative Determination of Protein in Cerebrospinal Fluid, *Arch. Int. Med.* 26:436 [Oct.] 1920) was used. The error of this method is not greater than 5 per cent. The spinal fluid was always removed under "basal" conditions.

3. The normal values are considered to be about 20 to 45 mg. per hundred cubic centimeters.

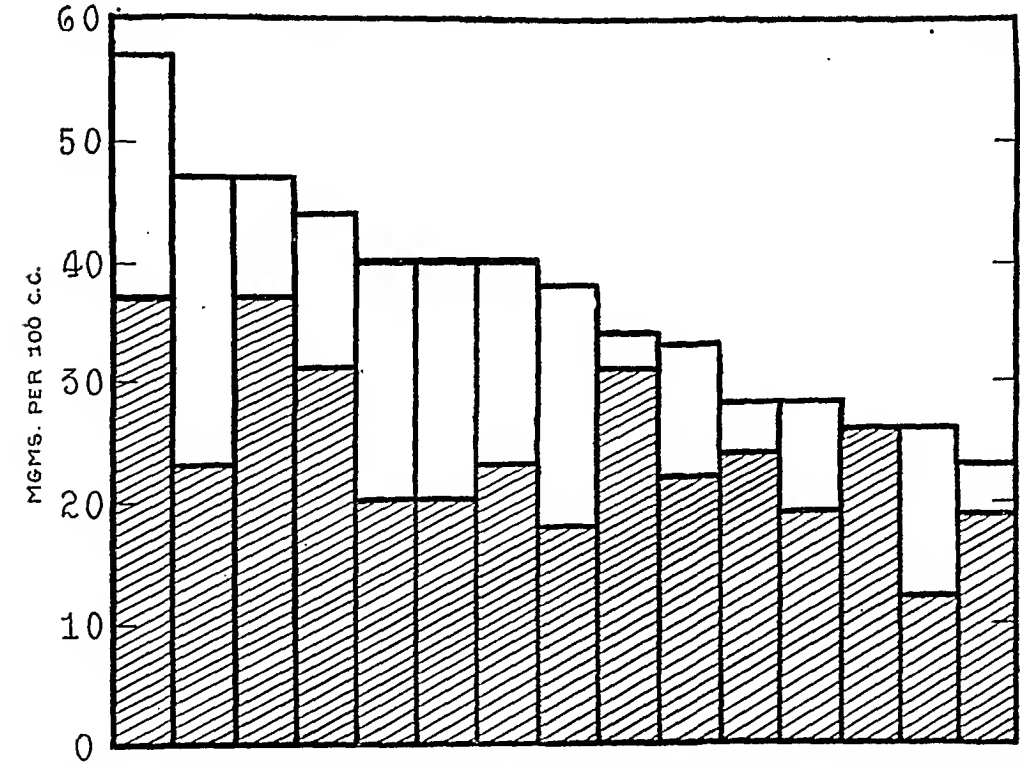
*The Concentration of Protein in Cerebrospinal Fluid in Fifteen Unselected Cases of Exophthalmic Goiter Before and After a Subtotal Thyroidectomy**

Patient			Before a Subtotal Thyroidectomy				After a Subtotal Thyroidectomy				
Age	Initials	Sex	Days Before Opera- tion	Basal Metabolic Rate, Per Cent Normal	Weight, Kg.	Concentration of Pro- tein in Spinal Fluid, Mg. per 100 Cc.	Days After Operation	Basal Metabolic Rate, Per Cent Normal	Weight, Kg.	Concentration of Pro- tein in Spinal Fluid, Mg. per 100 Cc.	Change in Protein Concentration, Mg. per 100 Cc.
42	P. M.	M	23	+63	62.2	37	78	+ 9	70.5	57	+20
38	J. B.	M	22	+52	51.3	23	70	- 6	61.8	47	+24
36	M. M.	F	13	+29	54.0	37	90	- 6	61.7	47	+10
38	M. O.	F	6	+18	66.3	31	103	-12	72.0	44	+13
17	B. D.	F†	7	+20	68.2	20	90	-21	71.7	40	+20
40	J. C.	M	69	+71	59.6	20	49	+33	72.3	40	+20
16	E. M.	F	19	+39	41.7	23	57	+ 2	52.5	40	+17
55	W. M.	M	24	+33	52.8	18	76	- 5	67.9	38	+20
18	E. F.	F	22	+57	43.6	31	37	- 7	45.5	31	+ 3
41	I. E. C.	M	21	+72	68.9	22	63	+20	68.5	33	+11
43	E. K.	M	18	+45	61.6	24	73	- 8	71.9	28	+ 4
18	V. G.	F†	7	+60	52.3	19	161	+29	55.4	28	+ 9
27	L. B.	M	22	+62	57.5	26	122	+ 8	70.5	26	0
42	A. G.	F†	10	+48	47.5	12	490	-19	55.7	26	+14
17	M. P.	F†	22	+35	43.1	19	104	+15	46.5	23	+ 4
Average...			..	+47	55.4	24	...	+ 3	63.2	37	+13

* In every instance, the concentration of protein recorded is that of the first 2 or 3 cc. removed from the lumbar region.

† In these two patients, the low basal metabolism after operation was not associated with an underfunction of the thyroid so far as could be clinically determined.

‡ In these instances two hemithyroidectomies were done, and the time after operation is the time after the second hemithyroidectomy. In V. G., the time before operation is the time before the second hemithyroidectomy; in M. P., it is the time before the first hemithyroidectomy.



The concentration of protein in spinal fluid in fifteen unselected cases of exophthalmic goiter, before (cross-hatched areas) and after (total height of columns) a subtotal thyroidectomy. The data are plotted in the order recorded in the table. In the thirteenth case, no change was noted.

The cause of these changes in protein concentration in myxedema and in exophthalmic goiter is uncertain. It has been previously suggested⁴ that they may be related in some manner to the increase in the storage of nitrogenous substances in myxedema and the apparent decrease in exophthalmic goiter.⁵ In any case, it seems to be satisfactorily established that the thyroid gland is an important factor in controlling the protein content of the cerebrospinal fluid.

It was observed that headaches following the lumbar punctures were more frequent before than after operation. Moreover, they were more frequent in patients with exophthalmic goiter preceding operation than in the patients with myxedema previously reported.¹

CONCLUSION

The concentration of protein in the cerebrospinal fluid is within the lower limits of normal in most cases of exophthalmic goiter and usually shows a well marked increase, in association with a gain in weight and reduction in basal metabolism following a subtotal thyroidectomy.

4. Footnote 1. Thompson, W. O.; Thompson, P. K.; Silveus, E., and Dailey, M. E.: The Cerebrospinal Fluid in Myxedema, *Arch. Int. Med.*, to be published.

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THE BASAL METABOLIC RATE IN RELATION TO THE MENSTRUAL CYCLE *

CLAIRE J. CONKLIN, M.S.

AND

J. F. McCLENDON, PH.D.

MINNEAPOLIS

As the previous work on the basal metabolic rate in relation to the menstrual cycle has been reviewed in practically every paper on the subject, we need mention only that of Griffith and his collaborators (1929).¹ Their results indicate a positive correlation. Although their data have not been treated statistically, the paper seems to be the best published to date. In the work described here, the Benedict-Roth apparatus was used. All the necessary precautions were observed in making the determinations. The determinations were made almost daily on ten different subjects throughout one or more menstrual cycles. The subjects were normal women without the complicating factor—menstrual pain (Boothby and Sandiford, 1924).² The surface areas were determined by the height-weight formula of DuBois.

In order to ascertain whether there is a relationship between the basal metabolic rate and the menstrual cycle, the cycle was divided into four periods: menstrual, postmenstrual, intermenstrual and premenstrual. The periods were considered of equal duration except in the case of the menstrual period, which is self-determined.

Table 1 gives the basal metabolic rate as determined. In table 2 the frequency distributions are shown with the average values for each period. Table 3 gives the standard deviation from the average for each series and the probable error of the average of each period of the cycle. The probable error of the average of each period is based on the standard deviation from the average for the series. The exception to this is the series for the entire group. In this case the probable error

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* From the Laboratory of Physiological Chemistry, University of Minnesota.

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2. Boothby, W. M., and Sandiford, I.: Basal Metabolism, *Physiol. Rev.* **55**:69, 1924.

TABLE 1.—*Basal Metabolic Rates*

Subject, M. G.; 20 Years; 1.58 Sq.M.				Subject, L. G.; 23 Years; 1.55 Sq.M.			
Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.	
Intermenstrual		Menstrual		Postmenstrual		Menstrual	
Feb. 12 34.0		Feb. 27 34.2		Feb. 16 31.5		Mar. 3 31.6	
13 34.4		28 33.4		17 31.9		4 30.9	
14 36.7		Mar. 1 32.2		18 33.3		5 31.6	
15 35.2		2 32.2		19 32.7		6 33.0	
Premenstrual		3 33.2		20 32.8		7 33.6	
16 33.8		4 32.8		21 31.6		8 30.0	
17 35.0		5 33.0		22 31.4		9 32.1	
18 33.5		6 32.6		23 32.5		10 32.3	
19 36.1		7 33.1		24 32.5		11 33.3	
20 36.7		8 34.0		25 33.7		Intermenstrual 12 31.1	
21 33.5		9 32.4		26 34.9		13 32.7	
22 33.4		10 32.8		27 33.9		14 32.3	
23 32.1		Intermenstrual 11 32.1		28 33.3		15 35.1	
24 33.6		12 33.0		Menstrual Mar. 1 31.8		16 31.8	
Menstrual				2 31.8			
25 32.7							
26 38.5							
Subject, M. S.; 35 Years; 1.67 Sq.M.				Subject, Eva S.; 22 Years; 1.64 Sq.M.			
Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.	
Postmenstrual		Premenstrual		Premenstrual		Postmenstrual	
Oct. 30 34.3		Nov. 17 36.7		Feb. 15 36.9		Mar. 2 36.9	
Nov. 1 35.5		18 35.5		16 33.5		4 34.4	
3 35.0		19 35.1		18 41.3		5 34.0	
5 35.5		20 36.5		19 42.7		6 31.6	
Intermenstrual		21 36.9		20 34.8		Intermenstrual 7 36.7	
7 34.9		22 36.4		21 36.0		8 31.4	
8 38.8		23 34.6		Menstrual		9 37.5	
9 33.1		24 35.4		22 36.3		12 34.6	
10 33.9		25 30.9		23 35.9		13 36.1	
11 35.4		26 33.8		25 31.5		14 37.0	
13 36.6		28 34.0		Postmenstrual 26 29.1		15 35.8	
Premenstrual		29 33.0		27 33.0		16 35.4	
14 37.3				28 33.9			
15 34.5				Mar. 1 36.0			
16 35.0							
Subject, E. T.; 20 Years; 1.73 Sq.M.				Subject, G. W.; 20 Years; 1.52 Sq.M.			
Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.	
Intermenstrual		Intermenstrual		Menstrual		Premenstrual	
Oct. 30 30.7		Nov. 21 35.0		Jan. 29 31.3		Feb. 18 33.2	
31 31.9		22 32.5		30 31.0		19 33.9	
Premenstrual		23 31.6		31 34.0		20 34.1	
Nov. 1 31.3		25 31.3		Feb. 1 34.3		21 32.7	
2 32.3		26 31.0		2 34.1		22 35.3	
3 31.3		27 28.7		3 33.2		Menstrual	
4 31.5		28 30.6		4 31.8		23 31.8	
5 33.2		29 30.2		Postmenstrual		24 30.6	
Menstrual		30 27.8		5 32.0		25 32.4	
6 30.9		Dec. 2 30.5		6 33.1		26 31.8	
7 31.0		3 29.7		7 33.7		27 31.8	
8 30.0		4 28.6		8 32.1		28 30.5	
9 30.1		5 28.1		9 33.1		Mar. 1 31.8	
10 31.2		6 30.9		10 30.5		2 30.5	
11 32.0		7 31.0		Intermenstrual 11 33.3		Postmenstrual	
Postmenstrual		8 29.5		12 30.0		3 30.9	
13 31.5		9 30.7		13 32.3		4 32.1	
15 31.0		10 29.4		14 32.4		5 33.7	
16 28.7		11 29.2		15 32.9		6 32.9	
Intermenstrual 17 30.1				16 32.3		7 30.9	
18 29.9				Postmenstrual 17 32.8		8 33.3	
19 30.7							
20 30.3							
Subject, C. C.; 22 Years; 1.63 Sq.M.							
Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.	
Postmenstrual		Postmenstrual		Intermenstrual		Intermenstrual	
Aug. 1 34.1		Aug. 24 32.8		Oct. 27 32.2		Nov. 21 28.8	
2 33.8		25 31.5		28 31.3		22 29.7	
3 33.9		27 34.1		29 32.1		Premenstrual	
Intermenstrual		28 34.5		30 31.9		23 29.2	
4 33.6		Oct. 10 34.3		31 30.1		24 30.2	
5 33.2		11 34.8		Nov. 1 31.5		25 31.2	
6 33.5		12 32.4		2 31.3		26 30.1	
7 32.6		13 32.3		3 33.4		27 28.0	
8 35.0		14 32.8		Menstrual		28 29.7	
9 35.1		15 34.4		8 31.9		Menstrual	
10 36.8		16 32.5		9 31.5		29 29.1	
Premenstrual		Postmenstrual 17 31.2		10 30.3		30 28.6	
11 33.5		18 31.3		Postmenstrual 11 32.6		Postmenstrual	
13 35.6		19 31.9		12 33.4		Dec. 1 29.2	
14 34.5		20 30.3		13 31.5		2 29.7	
15 35.7		21 32.0		14 30.8		3 29.8	
16 33.9		22 30.6		15 29.5		4 28.1	
17 33.7		23 30.1		16 29.1		5 27.8	
18 33.4		24 31.6		Intermenstrual 17 30.6		6 29.4	
Menstrual		25 31.6		18 32.1		7 29.8	
20 35.8		26 31.8		19 29.9		Intermenstrual	
21 31.7				20 30.0		8 29.7	
22 33.8						9 29.3	
23 32.7						10 30.3	
						11 33.3	

TABLE 1.—*Basal Metabolic Rates—Continued*

Subject, P. O.; 22 Years; 1.61 Sq.M.							
Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.		Calories per Sq.M. Date per Hr.	
Intermenstrual		Postmenstrual		Postmenstrual		Premenstrual	
July 31	32.8	Aug. 24	28.9	Oct. 27	29.4	Nov. 23	26.0
Aug. 2	31.6	25	29.0	28	31.0	Menstrual	24 32.4
3	31.7	Intermenstrual	27 29.6	29	29.8	25	29.7
4	30.7	28	27.8	30	30.9	26	27.7
Premenstrual	5 30.7	Oct. 10	31.2	31	31.3	27	29.0
6	30.4	11	31.0	Nov. 1	29.3	28	30.2
7	32.4	Premenstrual	12 30.3	2	30.2	Postmenstrual	30 28.8
8	31.9	13	30.9	3	28.6	Dec. 1	29.2
9	31.3	14	31.2	Intermenstrual	8 30.7	2	28.0
10	31.5	15	29.3	9	33.1	3	28.6
11	31.3	16	30.2	10	30.6	4	30.6
13	30.4	17	30.7	13	31.3	5	30.8
Menstrual	14 32.5	18	30.5	14	31.8	6	33.2
15	31.1	19	31.2	Premenstrual	15 30.3	7	30.8
16	30.0	20	31.8	16	30.4	8	30.1
17	28.9	Menstrual	21 30.1	17	30.6	Intermenstrual	9 28.9
Postmenstrual	18 30.5	22	30.8	18	31.7	10	29.9
20	30.9	23	30.6	19	29.2	11	29.3
21	30.2	24	32.2	20	29.4	12	29.4
22	31.0	25	30.0	21	29.4	13	30.6
23	29.3	Postmenstrual	26 32.3	22	30.6	14	28.8
Subject, E. S.; 21 Years; 1.48 Sq.M.							
Intermenstrual		Menstrual		Intermenstrual		Premenstrual	
Oct. 10	36.8	Oct. 24	37.0	Nov. 7	33.8	Nov. 21	37.1
11	35.5	25	37.2	8	38.1	22	38.1
12	37.1	26	35.6	9	37.5	23	39.0
14	38.1	27	36.6	10	38.3	24	38.8
15	36.3	28	37.0	11	37.3	Menstrual	25 36.4
Premenstrual	16 38.2	29	37.1	12	38.8	27	33.0
17	35.5	Postmenstrual	30 36.8	13	38.4	28	37.8
19	36.3	31	38.4	14	38.3	29	37.4
20	41.5	Nov. 1	36.3	15	36.6	Postmen- Dec. 1	33.7
21	38.9	2	36.6	Premenstrual	16 37.6	strual	2 39.1
22	38.1	3	36.5	18	36.4	3	36.3
23	37.5	4	33.3	19	38.9	4	38.2
		5	38.1	20	36.2	5	40.7
Subject, H. R.; 23 Years; 1.59 Sq.M.							
Menstrual		Intermenstrual		Premenstrual		Menstrual	
Feb. 5	33.5	Feb. 15	31.7	Feb. 23	30.9	Mar. 4	31.6
6	33.2	16	31.0	25	32.8	5	31.3
7	33.7	17	35.4	26	31.9	6	30.3
8	35.6	18	31.5	27	30.3	Postmenstrual	7 31.3
Postmenstrual	9 32.3	19	33.5	28	31.7	8	32.8
10	32.4	20	33.2	Menstrual Mar. 1	32.8	9	32.6
11	31.7	21	31.4	2	32.7	11	31.5
12	32.2	22	30.2	3	23.3	12	32.9
13	31.6						

of the average of each period is based on the standard deviation from the average of that period. It is only in this one case that the number of determinations warrants this treatment.

Chart 1 is simply a graphic representation of the daily determinations for each subject. Chart 2 shows the averages of table 2 plotted with respect to the probable errors of table 3. The rectangles represent the probable errors.

As noted in chart 2, the results indicate a definite trend toward a lowered rate either during or following menstruation and a premenstrual rise. This is especially significant in averages for the entire group. We cannot explain the one contradictory case, that of H. R.

In general, the curves obtained correspond to those of Wildebush and McClendon (1929) ³ for concentration of ovarian hormone in the circulating blood.

Included in the foregoing data is one special case—that of C. C. This subject was made a special case in order to eliminate the factors, diet and muscular activity, which affect the basal metabolic rate (Benedict, 1915 ⁴) (Helmreich, 1924 ⁵) (Wishart, 1927, 1928 ⁶).

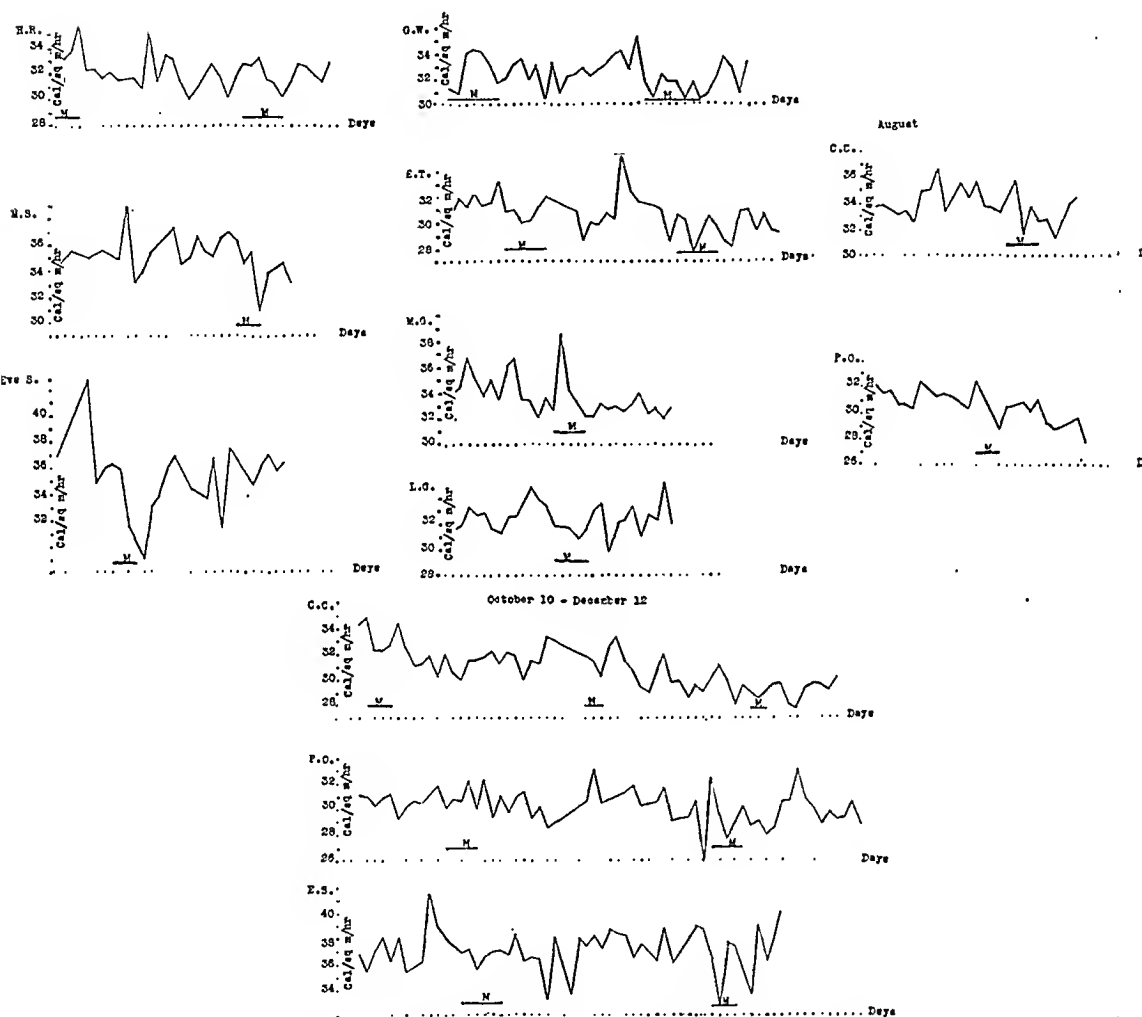


Chart 1.—Metabolic charts of the women studied.

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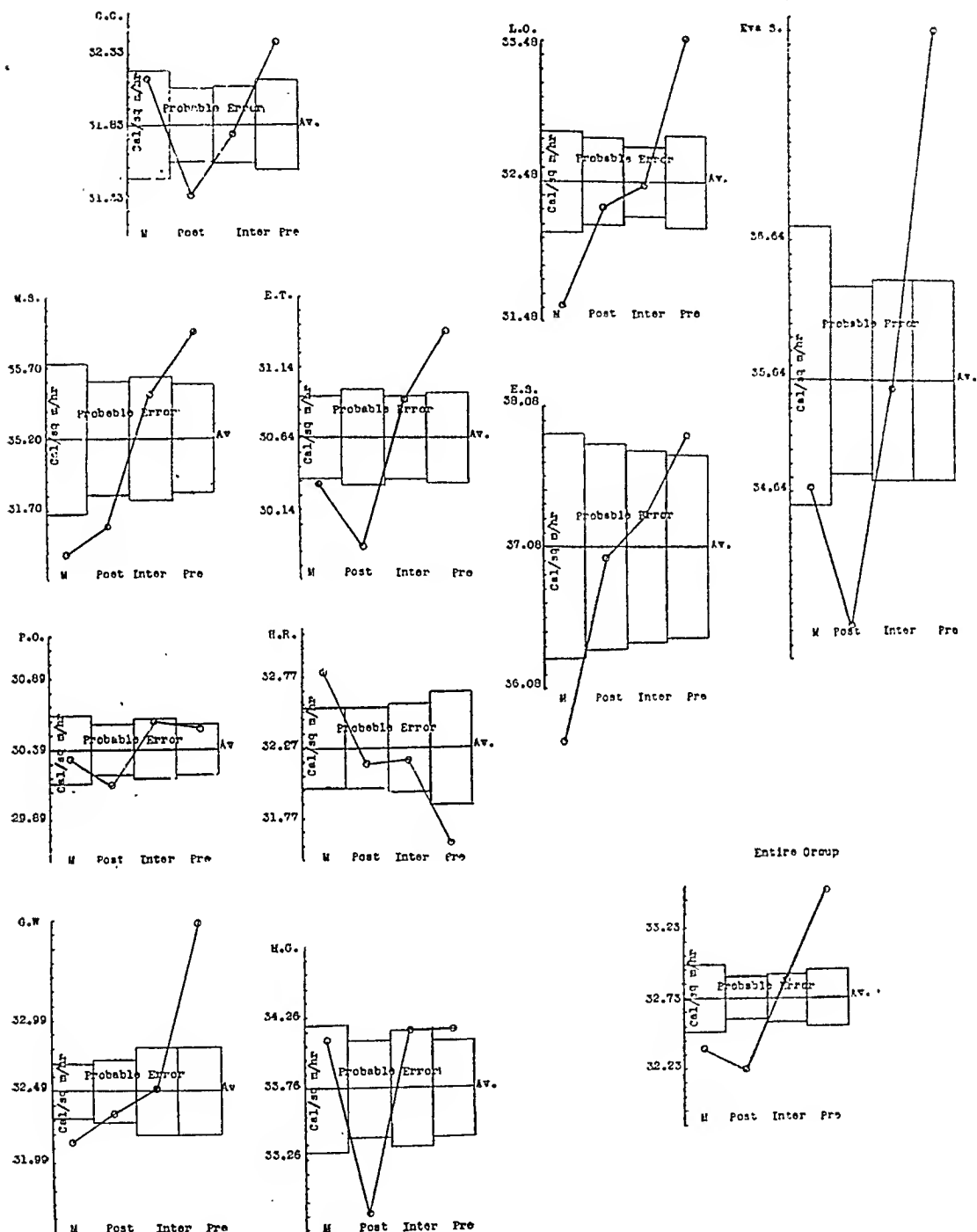


Chart 2.—Graph showing the variation in basal metabolic rate of women during the menstrual cycle. The calories per square meter per hour are noted on the ordinate and the periods—menstrual, postmenstrual, intermenstrual and premenstrual—on the abscissa. The circles denote the averages for the periods. The horizontal line denotes the grand average, and the rectangles denote the probable errors for the periods. Where the circle lies inside the rectangle, the results are within the probable errors and therefore do not show a significant variation from the grand average.

TABLE 2.—Frequency Distributions, with Average Values for Each Period

Subject H. R.	Calories per Sq. M. per Hour													No. of Deter- mina- tions	Average Calories per Sq. M. per Hour
	23	23.5	29.5	30	30.5	31	31.5	32	32.5	33	33.5	34	35		
Periods															
Menstrual.....	1	..	2	..	1	2	3	10	32.80
Postmenstrual.....	4	1	3	2	10	32.15
Intermenstrual.....	1	..	1	3	1	1	8	32.19
Premenstrual.....	1	1	1	1	..	1	5	31.60
Total.....	1	2	2	10	2	4	6	4	53	32.27
Subject M. G.															
Periods															
Menstrual.....	1	1	..	1	1	5	34.1
Postmenstrual.....	1	2	5	..	1	9	32.89
Intermenstrual.....	1	..	1	..	1	1	1	..	1	1	6	34.17
Premenstrual.....	1	4	1	1	1	1	9	34.17
Total.....	4	3	6	5	4	1	2	..	1	2	29	33.76
Subject G. W.															
Periods															
Menstrual.....	3	1	1	5	1	1	..	2	1	..	15	32.13
Postmenstrual.....	1	2	..	3	..	3	3	12	32.33
Intermenstrual.....	3	1	1	6	32.5
Premenstrual.....	1	2	..	2	6	33.67
Total.....	4	4	1	8	5	7	4	4	1	..	29	32.49
Subject L. G.															
Periods															
Menstrual.....	1	2	2	5	31.60
Postmenstrual.....	1	1	..	1	1	1	1	1	2	7	32.29
Intermenstrual.....	1	2	2	3	1	1	1	11	32.45
Premenstrual.....	2	2	..	2	1	..	6	33.50
Total.....	1	1	2	5	5	5	6	2	5	1	..	29	32.48

TABLE 2.--Frequency Distributions, with Average Values for Each Period--Continued

Subject P. O.	Periods	Calories per Sq. M. per Hour															No. of Determinations	Average Calories per Sq. M. per Hour
		26	26.5	27	27.5	28	28.5	29	29.5	30	30.5	31	31.5	32	32.5	33		
	Menstrual.....	1	2	1	4	1	2	..	1	2	..	14	30.32
	Postmenstrual.....	1	2	4	3	4	2	6	1	..	1	1	25	30.14
	Intermenstrual.....	1	..	2	3	1	4	2	3	1	..	2	19	30.58
	Premenstrual.....	1	1	3	1	10	3	4	2	1	..	26	30.51
	Total.....	1	1	2	2	9	10	10	17	13	8	4	4	3	84	30.39
Subject E. S.																		
Periods	Calories per Sq. M. per Hour															N (No. of Determinations)	X Calories per Sq. M. per Hour	
	33	33.5	34	34.5	35	35.5	36	36.5	37	37.5	38	38.5	39	40.5	41.5			
Menstrual.....	1	1	..	2	4	1	1	10	35.70	
Postmenstrual.....	..	2	4	1	..	2	1	1	1	..	12	37.00	
Intermenstrual.....	1	1	..	2	2	2	2	3	1	14	37.20	
Premenstrual.....	1	1	2	1	2	3	..	4	..	1	15	37.87	
Total.....	1	2	1	3	1	10	8	5	8	4	6	1	1	51	37.08	
Entire Group																		
Period																N (No. of Determinations)	X Calories per Sq. M. per Hour	
Menstrual																90	32.37	
Postmenstrual																125	32.22	
Intermenstrual																114	32.86	
Premenstrual																109	33.50	
Total.....																438	32.73	

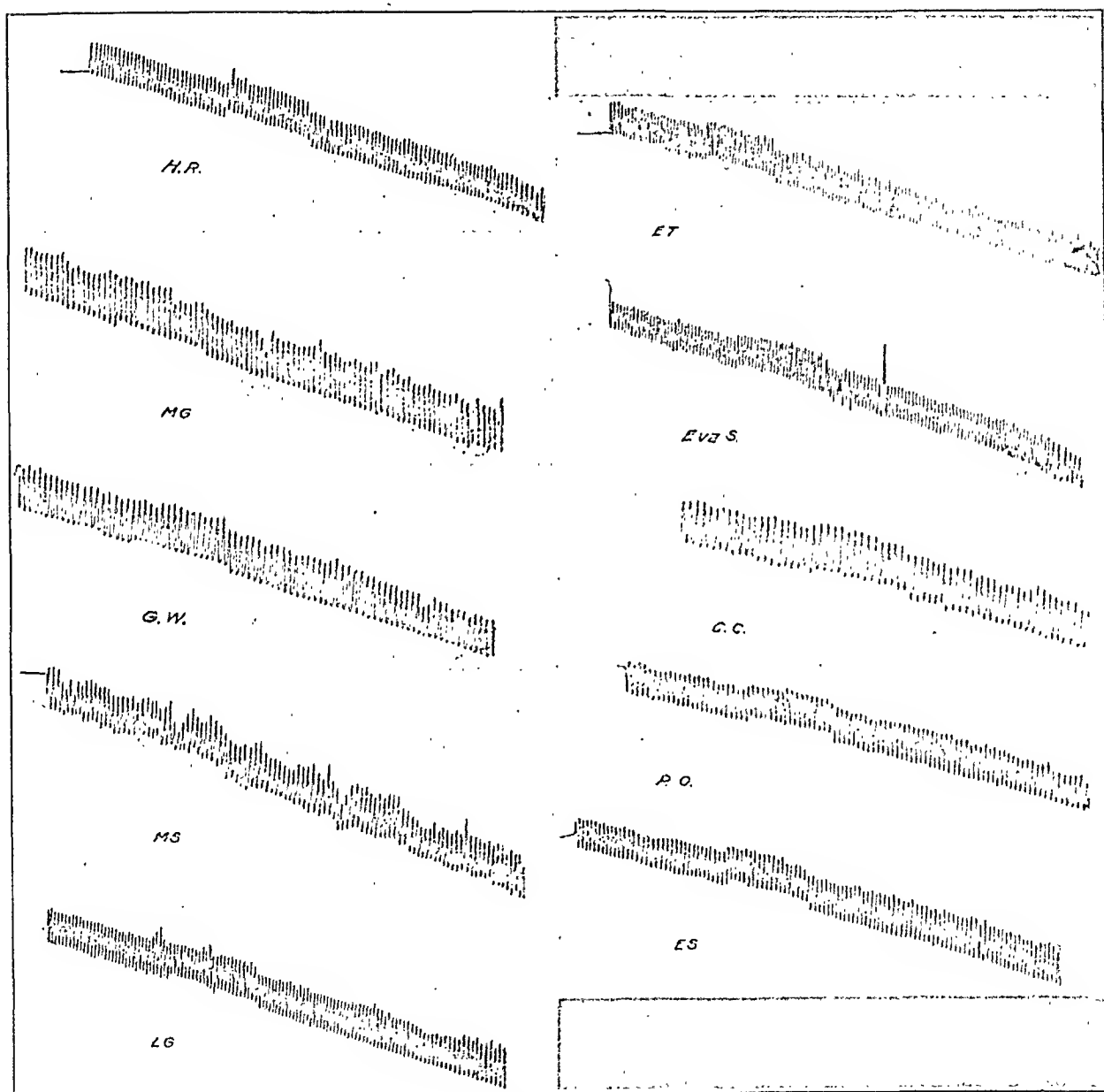


Chart 3.—Tracing on the Benedict-Collins apparatus during the characteristic respiratory habits of the ten women.

TABLE 3.—Standard Deviations from the Average for Each Series and Probable Error of the Average of Each Period of the Cycle

Subject	Menstrual		Postmenstrual		Intermenstrual		Premenstrual		Series: Average Calories per Sq.M. per Hour	Standard Deviation from Series (Aver.)
	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error	Average Calories per Sq.M. per Hour	Probable Error		
E. S.	35.70	±0.5016	37.00	±0.7817	37.29	±0.6774	37.87	±0.6545	37.08	3.7580
P. O.	30.32	±0.2418	30.14	±0.1809	30.58	±0.2076	30.54	±0.1774	30.39	1.3413
C. C.	32.15	±0.3793	31.33	±0.2632	31.77	±0.2682	32.42	±0.3223	31.83	2.0273
H. R.	32.80	±0.2780	32.15	±0.280	32.19	±0.3130	31.60	±0.3959	32.27	1.3126
Eva S.	34.67	±1.1008	33.88	±0.6741	35.57	±0.7206	38.14	±0.7206	35.64	2.8267
M. G.	34.10	±0.4502	32.89	±0.3356	34.17	±0.4110	34.17	±0.3356	33.76	1.4926
G. W.	32.13	±0.1944	32.33	±0.2174	32.50	±0.3074	33.67	±0.3074	32.49	1.1163
M. S.	31.38	±0.5332	34.57	±0.4031	35.50	±0.4354	35.94	±0.3771	35.20	1.581
E. T.	30.32	±0.2902	29.88	±0.3403	30.91	±0.2902	31.39	±0.3209	30.64	1.4271
L. G.	31.60	±0.3619	32.29	±0.3084	32.45	±0.2460	33.50	±0.3331	32.48	1.2097

Period	Entire Group		
	Average Calories per Sq.M. per Hour	Probable Error	Standard Deviation from Average
Menstrual.....	32.37	±0.2409	3.3887
Postmenstrual.....	32.22	±0.1475	2.4445
Intermenstrual.....	32.86	±0.1672	2.6472
Premenstrual.....	33.50	±0.1936	3.0736

From Oct. 4 to Dec. 11, 1928, subject C. C. lived on the following diet, weighed to the nearest gram:

Lunch

Eggs	100 Gm
Potatoes	100 Gm.
Crisco	10 Gm.
Butter	10 Gm.
Bread (whole wheat).....	200 Gm.
Milk	465 Cc.

Dinner

Vac-Dri Vegetable Mixture.....	30 Gm.
Dried beef.....	30 Gm
Canned tomatoes.....	150 Gm.
Bread (whole wheat).....	200 Gm.
Butter	10 Gm.
Loganberry jam (60 per cent dextrose)...	100 Gm.
Coffee	200 Cc.

Total ration, 1,200 Calories

During this period, subject C. C. did an almost invariable amount of routine work seven days each week.

The desired results were not obtained, since the diet proved to be slightly deficient in calories. The weight of the subject decreased about 7 per cent (9 pounds [4.1 Kg.]) during this period. The decrease in basal metabolic rate and duration of menstruation are well represented

in chart 1 for C. C., from October 10 to December 12. It is interesting to note that these effects were obtained on a diet so slightly deficient that the deficiency was not detected for about a month.

CONCLUSIONS

From this study it is concluded that:

1. The basal metabolic rate tends to reach its lowest level following menstruation and its highest level preceding menstruation.
2. A deficient diet decreases not only the basal metabolic rate but also the duration of menstruation and the length of the menstrual cycle.

CALCIUM METABOLISM IN ARTHRITIS *

E. F. F. COPP, M.D.

LA JOLLA, CALIF.

As the salts of lime form the greatest part of the inorganic portion of all the bones and of the teeth in the body, a study of the calcium metabolism in arthritis with bony changes is of interest. The mineral metabolism of the body is an important part of the general metabolism. Calcium salts are essential to most forms of life, and lime salts are present to a considerable amount in the tissues.

The present experimental study deals largely with the question of the calcium balance in the toxic type of arthritis. Two cases were studied intensively for many weeks. The first case was one of extensive hypertrophic osteo-arthritis in a woman, aged 60, who was more or less bedridden. The other patient was a woman, aged 55, who suffered from generalized atrophic osteo-arthritis. The following classification of arthritis is used.

- Rheumatic: By this term acute rheumatic fever only is meant.
Traumatic: Simplest form is synovitis such as housemaid's knee.
Hemorrhagic: Hemarthrosis is really a synovitis with hemorrhage into the joint.
This may occur in hemophilia.
Neuropathic: Charcot's: syringomelia of the spine.
Septic: Streptococci or staphylococcic infection of the joint introduced from the outside.
Infectious: From known systemic infections such as typhoid, pneumonia, influenza, tuberculosis, gonorrhea.
Toxic: (a) Hypertrophic osteo-arthritis
(b) Atrophic osteo-arthritis
(c) A combination of (a) and (b)
This last group includes the so-called rheumatoid arthritis and arthritis deformans. All cases show bony changes.

A great deal of interest is attached to the absorption, excretion and utilization of calcium salts. Lime salts being nearly all insoluble are absorbed with great difficulty from the stomach and intestinal tract and retard the absorption of fluid. They would have a cathartic action were it not for the fact that they are thrown out of solution by the alkaline salts. The greater portion of calcium when given by mouth as medicine undoubtedly leaves the body unabsorbed. When calcium is given intravenously there is an initial elevation of the blood calcium, but it is

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* From the Scripps Metabolic Clinic.

largely excreted. The excess calcium which is stored in some unknown locality in the body is gradually excreted.

In order to study the calcium balance it was necessary to determine the calcium intake and the calcium excretion. Calcium intake was chiefly in the form of food: milk, cheese and milk products, nuts, beets, egg-yolks and molasses contain high amounts of calcium. The calcium intake in the form of ordinary drinking water was negligible, but for

TABLE 1.—*Low Calcium Diet Used in Hypertrophic Osteo-Arthritis, Giving the Amounts of Inorganic Constituents Present as Well as the Total Calories*

Food	Grams	Protein	Fat	Carbo- hydrate	Calcium	Sodium Chloride	Magne- sium
Breakfast							
Grapejuice.....	100	0	0	16	0.0110	0.0030	0.0090
Cream, 20 per cent.....	30	1	6	2	0.0258	0.0390	0.0033
Butter, salt-free.....	20	0	17	0	0.0030	0.0260	0.0003
Puffed rice.....	15	1	0	12	0.0013	0.0188	0.0010
Egg.....	50	7	6	0	0.0335	0.0900	0.0055
Bacon.....	10	3	1	0	0.0011	0.1000	0.0118
White toast.....	10	1	0	6	0.0027	0.0700	0.0023
Total.....		13	30	36	0.0784	0.3418	0.0371
Lunch							
Butter, salt-free.....	10	0	9	0	0.0015	0.0130	0.0002
Salad							
Pineapple, canned.....	50	1	0	15	0.0090	0.0100	0.0055
Mayonnaise.....	20	0	17	0	0.0002	0.0028	0.0000
Blackberries.....	50	1	0	6	0.0085	0.0085	0.0105
White toast.....	10	1	0	6	0.0027	0.0700	0.0023
Butter, salt-free.....	20	0	17	0	0.0030	0.0260	0.0003
Egg plant.....	100	1	0	3	0.0110	0.0205	0.0150
Beef tongue.....	80	18	6	0	0.0104	0.0880	0.0914
Total.....		22	49	30	0.0463	0.2388	0.1282
Dinner							
Butter, salt-free.....	30	0	26	0	0.0045	0.0390	0.0005
Salad							
Asparagus.....	60	1	0	2	0.0150	0.0396	0.0066
Mayonnaise.....	20	0	17	0	0.0002	0.0028	0.0000
Peach, canned.....	80	1	0	24	0.0128	0.0048	0.0080
White toast.....	10	1	0	6	0.0027	0.0700	0.0023
Tomato.....	100	1	0	3	0.0110	0.0570	0.0100
Butter, salt-free.....	10	0	9	0	0.0015	0.0130	0.0002
Baked potato.....	100	2	0	18	0.0140	0.0650	0.0280
Roast veal.....	75	19	5	0	0.0105	0.0975	0.0885
Total.....		25	57	53	0.0722	0.3887	0.1441
Grand total.....		60	136	119	0.1969	0.9693	0.3094
Calories.....	1,940						

accurate observations distilled water was given. Distilled water was also used for the making of tea and coffee.

The calcium content of a diet can be varied from 200 to 2,000 mg. of calcium daily with perfect ease, at the same time giving the patient a well balanced, nourishing diet. Sample menus are given in tables 1 and 2.

The calcium metabolism of an arthritic patient can be studied and the diets changed as readily for content of mineral salts as the study of the tolerance of a diabetic patient for foods containing fat, protein and carbohydrate. The foods were accurately weighed, and any food

not eaten by the patient was reweighed in order to have accurate data. Any foods having a variable calcium content were preferably analyzed before being allowed in the diet. No medicine containing calcium was allowed at any time, unless experimentally, and then the calcium content was estimated. The figures of Friedenwald and Ruhräh,¹ of Sherman²

TABLE 2.—*High Calcium Diet Used in Atrophic Osteo-Arthritis, Giving the Amounts of Inorganic Constituents Present as Well as the Total Calories*

Food	Grams	Protein	Fat	Carbo- hydrate	Calcium	Sodium Chloride	Magne- sium	Iron
Breakfast								
Milk.....	200	6	8	10	0.2400	0.3200	0.0240	0.0005
Cream, 40 per cent.....	100	3	40	4	0.0360	0.1300	0.0100	0.0004
Butter, salt-free.....	20	0	17	0	0.0030	0.0060	0.0003	0.0000
Strawberries.....	150	2	0	11	0.0205	0.0150	0.0285	0.0012
Shredded wheat.....	30	3	0	23	0.0123	0.0333	0.0480	0.0015
Eggs.....	100	14	12	0	0.0670	0.1800	0.0110	0.0015
Bacon.....	20	7	2	0	0.0022	0.2000	0.0236	0.0030
Whole wheat bread....	30	3	0	16	0.0150	0.3090	0.0434	0.0005
Total.....		38	79	64	0.4460	1.1933	0.1888	0.0086
Lunch								
Milk.....	200	6	8	10	0.2400	0.3200	0.0240	0.0005
Cream, 20 per cent.....	50	2	10	3	0.0430	0.0650	0.0050	0.0002
Butter, salt-free.....	20	0	17	0	0.0030	0.0060	0.0003	0.0000
Salad								
Cottage cheese.....	50	11	1	2	0.4655	0.1000	0.0185	0.0006
Pineapple, canned....	100	1	0	30	0.0180	0.0200	0.0110	0.0005
Lettuce.....	20	0	0	0	0.0086	0.0250	0.0037	0.0001
Mayonnaise.....	20	0	17	0	0.0002	0.0416	0.0000	0.0000
Fresh cherries.....	200	2	0	34	0.0380	0.2060	0.0160	0.0008
Whole wheat bread....	20	2	0	10	0.0100	0.0100	0.0236	0.0004
Rhubarb sauce.....	100	1	0	30	0.0440	0.0000	0.0170	0.0010
Hubbard squash.....	100	1	0	9	0.0190	0.0500	0.0110	0.0006
Butter, salt-free.....	10	0	9	0	0.0015	0.0030	0.0000	0.0000
Bacon.....	20	7	2	0	0.0022	0.2000	0.0236	0.0030
Liver.....	100	23	4	0	0.0120	0.1400	0.1180	0.0540
Total.....		56	68	123	0.9050	1.1866	0.2747	0.0617
Dinner								
Buttermilk.....	200	6	2	10	0.2100	0.3500	0.0210	0.0005
Cream, 20 per cent.....	100	3	20	5	0.0560	0.1300	0.0100	0.0004
Butter, salt-free.....	30	0	26	0	0.0045	0.0090	0.0003	0.0000
Salad								
Dates.....	30	1	0	21	0.0150	0.0966	0.0230	0.0010
Grapefruit.....	100	1	0	5	0.0210	0.0050	0.0090	0.0003
Lettuce.....	20	0	0	0	0.0086	0.0250	0.0037	0.0001
Mayonnaise.....	10	0	9	0	0.0001	0.0208	0.0000	0.0000
Prunes.....	100	1	0	20	0.0540	0.0290	0.0550	0.0030
Whole wheat bread....	20	2	0	10	0.0100	0.0100	0.0236	0.0004
Spinach.....	150	2	0	5	0.1005	0.1875	0.0360	0.0027
Parsnip.....	100	1	0	14	0.0590	0.0510	0.0340	0.0006
Baked potato.....	100	2	0	18	0.0140	0.0657	0.0280	0.0013
Steak.....	90	21	14	0	0.0063	0.0990	0.1062	0.0145
Total.....		40	71	108	0.5890	1.0686	0.3558	0.0248
Grand total.....		134	218	300	1.9100	3.4485	0.8193	0.0951
Calories.....	3,698							

and those in Government Bulletin, No. 28 were used for the basis of the mineral content and food values in the diets. An excess of sodium chloride in the diets was avoided to prevent any undue increase in the

1. Friedenwald, J., and Ruhräh, J.: Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, p. 753.

2. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 2, New York, The Macmillan Company, p. 421.

absorption of calcium,³ and for the same reason diets high in carbohydrate were not given.⁴ Excesses of potassium and magnesium in the diet were not allowed, as these salts retard the absorption of calcium.⁵

Calcium excretion was mainly by the bowel in insoluble form. Approximately 90 per cent of the calcium was eliminated by the bowel and 10 per cent by the kidneys. Small amounts of calcium were eliminated by perspiration and exhalation. When phosphates were present in increased amount in the body, more of the calcium was excreted by the bowel as the insoluble calcium phosphate. If the chloride content of the body was high, more of the calcium was excreted in the urine as the soluble calcium chloride.

In order to determine the calcium output it was therefore necessary to make accurate daily twenty-four hour collections of the stools and urine for many weeks. Patients were chosen for this study who were not constipated in order that daily collections of the stools were obtained without the use of cathartics.

METHODS EMPLOYED

The estimation of the calcium in the stool and urine was made by the method of Kramer and Tisdall.⁶ In the determination of the calcium content of the stool, each whole stool was saved and evaporated over the water bath, and the air-dried weight of the whole stool was used as the basis for the determination of the calcium. Two grams of powdered stool was used in each case for the actual calcium determination. In the determination of the calcium content of the urine 100 cc. from the twenty-four hour collection was evaporated to dryness over the water bath, and the residue was used as the further basis for the determination.

During the course of this study, a determination of the calcium content of the blood was made in fifty normal cases. The method of Kramer and Tisdall⁷ was again used. The older methods used in determination of the calcium in the blood included various types, gravimetric, colorimetric, nephelometric and volumetric, and the values reported varied tremendously. Most of the blood calciums were allowed to be precipitated twenty-four hours before the determination. The specific time of thirty minutes was allowed in all of the present determinations. For an excellent review of the literature on calcium metabolism the reader is referred to an article by Stewart and Percival.⁸ The

3. Richards, Godden and Husband: *Biochem. J.* **18**:651, 1924.

4. Bergeim, O.: *J. Biol. Chem.* **70**:35, 1926.

5. Bogert, L. J., and McKittrick, E. J.: *J. Biol. Chem.* **54**:363, 1922.

6. Kramer, B., and Tisdall, F. F.: *J. Biol. Chem.* **48**:1, 1921.

7. Kramer, B., and Tisdall, F. F.: *J. Biol. Chem.* **47**:475, 1921.

8. Stewart, C. P., and Percival, G. H.: *Physiol. Rev.* **8**:283, 1928.

calcium determinations were all done on the serum calcium which was nonhemolized, and duplicate determinations were made. Hemolysis of the red blood cells invariably resulted in obtaining a lower figure for the serum calcium. In a series of fifty normal persons it was found that the serum calcium ranged from 9 to 10.4 mg. per hundred cubic centimeters of nonhemolized serum. In an analysis of 200 patients the highest serum calcium found was 12.2 mg. per hundred cubic centimeters in a case of hypertrophic osteo-arthritis. Of fourteen patients with hypertrophic osteo-arthritis, ten had serum calciums above 10.5 mg. per hundred cubic centimeters, and in four it fell within the normal limit. Five patients with chronic glomerular nephritis, all in the end-stage but not moribund nor dehydrated, showed low serum calciums ranging from 6.8 to 8.2 mg. per hundred cubic centimeters. One patient with multiple myeloma had a blood calcium of 17 mg. per hundred cubic centimeters of serum, and another patient with carcinoma of the prostate with extensive rarefaction of the pelvic bones with metastases had a blood calcium of 16.5 mg. In the dog, distinctly higher blood calciums were found. In a series of more than 100 determinations on normal dogs, the serum calcium ranged from 10.8 to 12 mg. per hundred cubic centimeters.

EXPERIMENTAL DATA

In table 3 are recorded certain data obtained from the case of hypertrophic osteo-arthritis. In the first column the calcium intake for each day is charted, followed in the second column by the daily calcium excretion in the stool and in the third column by the daily calcium excretion in the urine. The fourth column gives the total calcium excretion for each day. In the last column the daily calcium balance is tabulated.

For the first four weeks this patient was given a general diet, and during the last two weeks the calcium metabolism was followed: During that time there was a retention of 1.178 Gm. of calcium in the system. For the next week a diet not exceeding 200 mg. of calcium daily was given, and it was found that there was a negative calcium balance and 2.575 Gm. of calcium was lost from the system. For the next nine days the same low calcium diet was given, but 20 drops of 10 per cent hydrochloric acid were administered three times a day before meals. The effect of the hydrochloric acid was to increase the percentage of calcium excretion by the urine and to decrease slightly the total amount of calcium lost from the system. For the following six days the same dosage of phosphoric acid was given, and although the calcium excretion by the urine was in the same proportion as when hydrochloric acid was used there was decidedly less calcium lost from

TABLE 3.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Hypertrophic Osteo-Arthritis*

Date	Calcium Intake, Gm.	Calcium In Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
General Diet					
January 24.....	0.658	0.764	0.078	0.842	-0.184
25.....	1.164	0.542	0.074	0.616	+0.548
26.....	0.921	0.648	0.072	0.720	+0.201
27.....	0.593	0.642	0.066	0.708	-0.112
28.....	0.886	0.598	0.078	0.676	+0.210
29.....	0.599	0.624	0.074	0.698	-0.099
30.....	0.871	0.594	0.080	0.674	+0.197
31.....	0.636	0.820	0.062	0.882	-0.246
February 1.....	0.661	0.764	0.069	0.833	-0.172
2.....	0.545	0.521	0.063	0.587	-0.042
3.....	0.564	0.466	0.069	0.535	+0.029
4.....	0.933	0.449	0.076	0.525	+0.408
5.....	1.167	0.450	0.074	0.524	+0.643
6.....	0.699	0.832	0.070	0.902	-0.203
	10.900	8.714	1.008	9.722	+1.178
Low Calcium Diet					
February 7.....	0.145	0.542	0.052	0.594	-0.449
8.....	0.181	0.648	0.059	0.707	-0.523
9.....	0.147	0.541	0.052	0.593	-0.446
10.....	0.151	0.403	0.051	0.454	-0.303
11.....	0.187	0.246	0.042	0.288	-0.101
12.....	0.205	0.344	0.068	0.412	-0.207
13.....	0.204	0.695	0.055	0.750	-0.546
	1.223	3.419	0.379	3.798	-2.575
Low Calcium Diet with 10 per Cent Hydrochloric Acid, 20 Drops Three Times Daily Before Meals					
February 14.....	0.194	0.346	0.039	0.385	-0.191
15.....	0.153	0.300	0.050	0.350	-0.197
16.....	0.177	0.176	0.047	0.223	-0.046
17.....	0.144	0.940	0.057	0.997	-0.853
18.....	0.200	0.427	0.057	0.484	-0.284
19.....	0.200	0.400	0.063	0.553	-0.353
20.....	0.181	0.162	0.066	0.228	-0.047
21.....	0.188	0.332	0.062	0.394	-0.206
22.....	0.197	0.344	0.034	0.378	-0.181
	1.634	3.517	0.475	3.092	-2.358
Low Calcium Diet with 10 per Cent Phosphoric Acid, 20 Drops Three Times Daily Before Meals					
February 23.....	0.173	0.342	0.032	0.374	-0.201
24.....	0.196	0.226	0.030	0.256	-0.060
25.....	0.152	0.164	0.028	0.192	-0.040
26.....	0.199	0.216	0.031	0.247	-0.048
27.....	0.193	0.168	0.021	0.189	+0.004
28.....	0.190	0.159	0.034	0.193	-0.003
	1.103	1.275	0.176	1.451	-0.348
Low Calcium Diet with Sodium Salicylate, 15 Grains, Three Times Daily Before Meals					
March 1.....	0.199	0.212	0.038	0.250	-0.051
2.....	0.193	0.293	0.042	0.340	-0.142
3.....	0.190	0.322	0.054	0.376	-0.186
4.....	0.166	0.314	0.058	0.372	-0.206
5.....	0.181	0.316	0.066	0.382	-0.201
6.....	0.175	0.420	0.060	0.480	-0.305
7.....	0.157	0.301	0.052	0.353	-0.196
8.....	0.193	0.332	0.048	0.389	-0.187
9.....	0.199	0.241	0.055	0.296	-0.097
10.....	0.208	0.357	0.050	0.407	-0.199
	1.896	3.113	0.523	3.636	-1.740
Same Diet but with Sodium Bicarbonate, 10 Gm., Three Times Daily Before Meals					
March 11.....	0.161	0.379	0.016	0.425	-0.264
12.....	0.195	0.401	0.042	0.443	-0.248
13.....	0.152	0.412	0.031	0.443	-0.311
14.....	0.203	0.444	0.038	0.482	-0.279
15.....	0.200	0.506	0.032	0.428	-0.228
16.....	0.194	0.493	0.049	0.542	-0.348
	1.085	2.525	0.238	2.763	-1.678

the system. The diet still was the same low calcium diet (200 mg. daily) (table 1). For the next ten days the patient was given 15 grains (0.972 Gm.) of sodium salicylate three times daily in place of the phosphoric acid. This time there was a marked increase in the urine calcium accompanied by an increased total excretion of calcium more comparable to the total calcium excreted during the period in which hydrochloric acid was given. Finally, for six days sodium bicarbonate was administered in 10 Gm. doses three times a day before meals. During this period, the amount of calcium excreted by the urine was markedly decreased although the total calcium excreted was again increased and 1.678 Gm. of calcium was lost from the system.

During the whole period, the blood calcium remained almost constant, being the highest, 11.2 mg. per hundred cubic centimeters, on January 24, and the lowest, 10.8 mg. per hundred cubic centimeters, on March 8. The carbon dioxide combining power of the plasma and the red blood count were normal throughout.

It was noted that the calcium equilibrium was changed from a positive to a negative balance by means of a diet low in calcium. Phosphoric acid greatly retarded the loss of calcium from the system, much more so than hydrochloric acid or sodium salicylate. Sodium salicylate markedly increased the amount of calcium excreted in the urine. Hydrochloric acid and phosphoric acid also increased the percentage of calcium eliminated by the urine but to a less degree. Sodium bicarbonate increased the total amount of calcium lost from the system and markedly decreased the amount of calcium excreted in the urine.

The second case studied was one of atrophic osteo-arthritis (table 4). As the x-ray pictures in this case showed a marked loss of lime salts from the bones of the body, while in the first case an increased density was reported, as nearly as possible a duplicate study of this patient was made for comparative purposes. For the first eleven days the patient was given a general diet, and during this time there was a loss of 4.881 Gm. of calcium from the system. For the following five days a diet low in calcium was employed and there was such a marked loss of calcium noticed that on this account a diet moderately high in calcium and moderately high in calories was next given. On this diet, a negative calcium balance was changed to a positive balance, and in ten days there was a retention of 3.694 Gm. of calcium. For the next two weeks a diet high in calcium was given, and the calcium balance became still more positive (table 4). Up to this time no medication had been given.

Dilute phosphoric acid in doses of 20 drops before meals was given for the following twelve days. During this period, the calcium balance

TABLE 4.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Atrophic Osteo-Arthritis*

Date	Calcium Intake, Gm.	Calcium in Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
General Diet; No Medication					
March 22.....	0.440	0.942	0.056	1.028	—0.588
23.....	0.684	0.858	0.120	0.978	—0.294
24.....	0.406	0.902	0.104	1.006	—0.600
25.....	0.428	0.584	0.119	0.703	—0.275
26.....	0.475	0.811	0.255	1.066	—0.621
27.....	0.410	0.768	0.123	0.911	—0.501
28.....	0.708	0.659	0.111	0.770	—0.662
29.....	0.673	2.137	0.171	2.308	—1.635
30.....	0.461	0.232	0.240	0.472	—0.011
31.....	0.589	0.526	0.264	0.790	—0.201
April 1.....	0.631	0.464	0.260	0.724	—0.693
	5.905	8.933	1.853	10.786	—4.881
Low Calcium Diet; No Medication					
April 2.....	0.195	0.502	0.157	0.659	—0.463
3.....	0.237	0.421	0.108	0.619	—0.382
4.....	0.184	0.567	0.094	0.661	—0.477
5.....	0.207	0.353	0.072	0.425	—0.218
6.....	0.175	0.458	0.128	0.586	—0.411
	0.999	2.301	0.649	2.950	—1.951
General for Calcium but Moderately High Caloric Diet; No Medication					
April 7.....	0.984	0.179	0.149	0.328	+0.656
8.....	1.339	0.258	0.176	0.434	+0.905
9.....	1.350	0.302	0.082	0.384	+0.966
10.....	0.893	0.957	0.153	1.140	—0.242
11.....	0.603	0.215	0.084	0.290	+0.304
12.....	1.305	0.524	0.072	0.596	+0.709
13.....	0.891	0.720	0.036	0.756	+0.135
14.....	0.868	0.804	0.046	0.850	+0.018
15.....	0.825	0.650	0.116	0.766	+0.059
16.....	0.863	0.560	0.124	0.684	+0.184
	9.931	5.199	1.038	6.237	+3.694
High Calcium Diet; No Medication					
April 17.....	2.23	0.633	0.052	0.685	+1.545
18.....	1.60	0.414	0.054	0.468	+1.132
19.....	2.18	0.550	0.090	0.640	+1.540
20.....	1.39	0.473	0.045	0.518	+0.872
21.....	2.13	1.876	0.040	1.916	+0.214
22.....	2.12	1.094	0.083	1.177	+0.943
23.....	1.94	0.555	0.083	0.638	+1.362
24.....	2.09	1.920	0.255	2.175	—0.085
25.....	2.20	2.056	0.051	2.107	+0.093
26.....	1.43	2.278	0.138	2.416	—0.956
27.....	1.29	1.642	0.186	1.828	—0.538
28.....	1.95	1.408	0.039	1.447	+0.503
29.....	1.81	1.821	0.073	1.894	—0.084
	24.36	16.720	1.189	17.909	+6.451
High Calcium Diet with 10 per Cent Phosphoric Acid, 20 Drops Three Times Daily Before Meals					
April 30.....	2.088	1.082	0.059	1.141	+0.947
May 1.....	1.798	1.123	0.105	1.228	+0.570
2.....	1.571	0.533	0.102	0.635	+0.936
3.....	2.483	0.720	0.258	0.978	+1.505
4.....	1.779	1.011	0.211	1.222	+0.557
5.....	1.897	0.842	0.108	0.950	+0.947
6.....	1.724	1.118	0.059	1.177	+0.547
7.....	1.350	0.833	0.154	0.987	+0.363
8.....	0.595	0.789	0.210	0.990	—0.404
9.....	1.168	0.845	0.338	1.183	—0.015
10.....	1.861	1.080	0.336	1.416	+0.445
11.....	1.857	0.821	0.067	0.888	+0.969
	20.171	10.797	2.007	12.804	+7.367

TABLE 4.—*The Changes in the Calcium Balance Noted as a Result of Dietetic and Drug Therapy Obtained in a Case of Atrophic Osteo-Arthritis—Continued*

Date	Calcium Intake, Gm.	Calcium in Stool, Gm.	Calcium in Urine, Gm.	Calcium Output, Gm.	Calcium Balance, Gm.
High Calcium Diet with Sodium Bicarbonate, 10 Gm. Three Times Daily Before Meals					
May 12.....	1.913	1.401	0.260	1.661	+0.282
13.....	1.864	1.193	0.118	1.311	+0.553
14.....	1.874	1.016	0.100	1.176	+0.698
15.....	2.351	1.057	0.276	1.333	+1.018
16.....	1.914	1.344	0.079	1.423	+0.491
17.....	0.407	1.754	0.052	1.806	-1.399
18.....	2.179	1.022	0.087	1.109	+1.070
19.....	1.285	1.044	0.078	1.122	+0.163
20.....	1.651	0.644	0.092	0.736	+0.915
	15.468	10.475	1.202	11.667	+3.791
High Calcium Diet with 10 per Cent Hydrochloric Acid, 20 Drops Three Times Daily Before Meals					
May 21.....	1.135	0.428	0.244	0.672	+0.463
22.....	1.856	0.515	0.383	0.928	+0.923
23.....	2.538	1.260	0.398	1.658	+0.880
24.....	1.508	1.204	0.297	1.501	+0.007
25.....	1.860	1.800	0.501	2.301	-0.441
26.....	2.316	1.254	0.460	1.731	+0.582
27.....	1.518	0.355	0.352	0.707	+0.811
28.....	2.673	1.434	0.380	1.814	+0.859
29.....	0.687	1.227	0.220	1.447	-0.860
30.....	1.909	0.657	0.267	0.924	+0.935
31.....	1.694	1.039	0.336	1.375	+0.319
June 1.....	2.090	0.595	0.307	0.902	+1.188
2.....	2.311	1.770	0.365	2.135	+0.176
	23.995	13.568	4.530	18.098	+5.897
High Calcium Diet with Sodium Salicylate, 15 Grains Three Times Daily Before Meals					
June 3.....	1.794	0.897	0.220	1.117	+0.677
4.....	2.226	1.036	0.372	1.408	+0.818
5.....	1.927	1.242	0.302	1.544	+0.383
6.....	2.121	0.664	0.376	1.040	+1.081
7.....	2.500	1.104	0.267	1.371	+1.129
8.....	0.722	1.211	0.341	1.552	-0.830
9.....	1.367	0.623	0.426	1.049	+0.318
10.....	2.102	0.763	0.410	1.173	+0.929
11.....	2.150	1.140	0.396	1.536	+0.614
12.....	1.780	1.252	0.415	1.667	+0.113
13.....	2.532	1.021	0.332	1.333	+1.179
14.....	1.984	1.418	0.254	1.672	+0.312
15.....	1.836	1.629	0.444	2.073	-0.237
16.....	1.305	1.001	0.526	1.527	-0.222
17.....	2.080	0.762	0.472	1.234	+0.846
	28.426	15.763	5.553	21.316	+7.110

became most markedly positive, and 7.367 Gm. of calcium was retained. For the next nine days, during which time sodium bicarbonate was given in doses of 10 Gm. before meals, the calcium balance was much less positive. There was a marked reduction in the calcium excretion in the urine, the amount falling as low as 10.3 per cent as compared to that of 16 per cent obtained while phosphoric acid was being administered. Dilute hydrochloric acid was then given in doses of 20 drops before meals. During this period of thirteen days, the amount of calcium excreted by the kidneys went to 25 per cent of the total excretion. There was less calcium lost from the system than during the period that sodium bicarbonate was given, but more calcium was excreted than during the use of phosphoric acid. During the final

ten day period, sodium salicylate was given in doses of 15 grains three times daily before meals. The calcium excretion in the urine rose to approximately 26 per cent of the total. This was the highest relative amount to be excreted in the urine in both cases. The calcium balance remained approximately the same as there was less calcium found in the stools.

During the total period of observation, the serum calcium remained practically constant at 10.8 mg. per hundred cubic centimeters, and the blood counts did not change appreciably. On two occasions, for a period of a week, the nitrogen excreted in the urine exceeded the intake, but when more protein was allowed in the diet nitrogenous equilibrium resulted. The type of diet used in this case is given in table 2.

TABLE 5.—*Tabulation for Comparative Purposes, Showing the Changes in the Calcium Balance Obtained in Hypertrophic and Atrophic Osteo-Arthritis*

		Hypertrophic Osteo-Arthritis		
Diet	Medication	Calcium in Stool, per Cent of Total	Calcium in Urine, per Cent of Total	Average Daily Calcium Balance, Gm.
General	89.6	10.4	+0.084
Low calcium	90.1	9.9	-0.363
Low calcium	10 per cent hydrochloric acid, 20 drop three times daily	88.1	11.9	-0.262
Low calcium	10 per cent orthophosphoric acid, 20 drops three times daily	87.9	12.1	-0.058
Low calcium	Sodium salicylate, 15 grains three times daily	85.6	14.4	-0.174
Low calcium	Sodium bicarbonate, 10 Gm. three times daily	91.4	8.6	-0.279
		Atrophic Osteo-Arthritis		
General	82.9	17.1	-0.444
Low calcium	78.0	22.0	-0.299
High caloric	83.3	16.7	+0.369
High calcium	93.4	6.6	+0.500
High calcium	10 per cent orthophosphoric acid, 20 drops three times daily	81.0	19.0	+0.614
High calcium	Sodium bicarbonate, 10 Gm. three times daily	89.7	10.3	+0.420
High calcium	10 per cent hydrochloric acid, 20 drops three times daily	75.0	25.0	+0.451
High calcium	Sodium salicylate, 15 grains three times daily	74.0	26.0	+0.474

Table 5 is a summary of tables 3 and 4 and shows the type of diet used, the medication and the average daily percentage of calcium excreted in the stool and in the urine, and also gives the average daily calcium balance.

SUMMARY

1. The daily calcium metabolism in two cases of toxic arthritis was studied for many weeks.

2. A retention of calcium was found in the patient with hypertrophic osteo-arthritis.

3. A loss of calcium or a negative calcium balance existed in the patient with atrophic osteo-arthritis.

4. The calcium balance was altered by dietetic means.

5. The effect on the calcium balance of several medicines commonly used in the treatment for arthritis was observed.

6. Phosphoric acid caused a retention or a better utilization of calcium.

7. All acids used increased the proportionate amount of calcium excreted in the urine.

THE PERIPHERAL SURFACE TEMPERATURE IN ARTHRITIS *

LILLIE M. WRIGHT, M.A.

AND

RALPH PEMBERTON, M.D.

PHILADELPHIA

Interest in the problem of arthritis is increasing. This is owing partly to the fact that insurance of the working classes, especially in Europe, is forcing the problem *de novo* on the medical conscience, and partly to the internal growth of the topic through the efforts of the relatively small number of persons who have for some years been investigating the disease. This number is now growing, however. A wider outlook on the problem of arthritis is also being developed. The important advance chronicled by the search for and removal of focal infections, not only in arthritis but in many diseases, has often had the incidental effect of directing attention away from those departures in physiology which actually constitute the disease syndrome. This has been less the case in Europe than in this country. It is probably fair to say that the emphasis placed on focal infection in America has achieved a meticulousness of technic which in general exceeds that available elsewhere and has consequently had more signal success. In Europe, the attitude of the profession has been somewhat less crystallized toward the problem, and has therefore included more consideration of the other factors operative to produce rheumatoid disability such as heredity, age, bodily constitution, the climacteric, exposure, intestinal dysfunction and the food intake. In this respect, the European point of view represents a wider range of vision than has been maintained, in general, in this country.

Close students of arthritis realize that after giving infectious factors their fullest value from both the etiologic and the therapeutic standpoint, there is a large and distressing number of sufferers from arthritis who cannot be benefited along this line of attack. Even if it be postulated, for the sake of argument, that all cases of arthritis of every variety are due to infection and that such infection is invariably of a single specific nature, it is obvious that one is a long way from being able to apply, in an adequately successful manner, therapy based on this concept. As a matter of fact, however, it is common knowledge

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* From the Laboratory of Clinical Chemistry, Presbyterian Hospital.

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that not only is there a great difference of opinion among students of the disease as to the importance of the rôle played by infection in the several forms of arthritis, especially hypertrophic arthritis, but, even when infectious processes are acceptedly concerned, it is again common knowledge that many varieties of organisms may be operative. These varieties include not only the many strains of streptococcus (viridans, hemolyticus, nonhemolyticus and intermediary forms), but also such organisms as the gonococcus, staphylococcus, colon bacillus, pneumococcus and others.

In view of the foregoing considerations, it can hardly be doubted that there is need for information bearing on the disturbances in physiology, whatever their etiology, productive of the phenomena and symptoms of the disease. Even in tuberculosis and syphilis, concerning which knowledge of the etiologic factors is relatively clearcut, study of the deviations of physiology accompanying the disease cannot be ignored; and, in point of fact, the treatment for tuberculosis rests today chiefly on empiric and physiologic, rather than purely bacteriologic, considerations.

It is apparently necessary to point out, in some quarters, the fact that study of the physiologic background of arthritis carries no implication of any lesser importance to be attached to such infectious factors as are known to be operative. When these are the exciting agents, the influence of bacteria in the production of arthritis is in no way comparable to the gross depredations of the tubercle bacillus and pus-forming organisms in inducing, for example, liquefaction necrosis. The influence of bacteria in arthritis is achieved, in general, by a more subtle mechanism. Study of this mechanism would probably lead to better, if not complete, understanding of the problem of arthritis and of some other conditions as well. To jump from interest in some of the etiologic factors of arthritis to consideration of only the clinical end-phenomena of the disease is largely to ignore study of the essential disease itself. It is fortunate that the door is now more widely opened for entrance on this phase of study of the problem.

The observations to be recorded have been carried out from the general standpoint just outlined. Within the last eight years we¹ have adduced increasing evidence pointing to the fact that there is in the arthritic syndrome a tendency toward a disturbance of peripheral blood flow which constitutes part of, if not part of the cause of, the objective phenomena of the disease. This evidence has been based somewhat on direct observations of the capillary beds,² to be reported elsewhere in

1. Pemberton, Ralph; Hendrix, B. M., and Crouter, C. Y.: *J. Metab. Research* **2**:301, 1922.

2. Pemberton, Ralph: *Arthritis*, *J. Michigan M. Soc.* **26**:599, 1927.

detail, and somewhat on observations of the red cell count in blood obtained from peripheral regions.³ Other considerations, which cannot be detailed here,⁴ strengthen the belief that the peripheral circulation is concerned in the phenomena of arthritis, and it becomes important accordingly to obtain, if possible, further corroboratory data. If there is in arthritis, as has been advanced by us, a tendency toward a sluggish peripheral blood flow and consequent "anemia" or "anoxemia" of the tissues, some expression of this should be found in terms of the local temperature of the part. According to Lewis,⁵ there are three methods available for the study of cutaneous circulation: direct microscopic observation, study of the skin color and its changes and study of the skin temperature and its response to various influences. Local temperature is presumably a function of heat production, heat loss and blood flow. In the absence of evidence suggesting disturbance of heat production, and under apparently comparable conditions of heat loss as regards normal and arthritic subjects, changes of temperature at the periphery of arthritic patients can be referred with considerable confidence to changes in the amount or rate of blood flow in the part concerned. It is true that about one fifth of the arthritic patients studied chiefly in the army, and of the atrophic type, showed a lower basal metabolic rate.^{5a} It has also been shown, however, by direct calorimetry,⁶ that there is no abnormal respiratory metabolism following the ingestion of large test meals of carbohydrate and protein, and the lowered basal metabolic rate encountered in one fifth of arthritic patients is probably to be explained along more mechanical lines. It appears, indeed, to be a reflection of the disturbance of blood supply to many tissues, especially the muscles.^{6a} Furthermore, coincident observations already reported in a preliminary way,² based on direct inspection of the capillaries, add strong evidence that the surface temperature under the conditions of study is referable chiefly or wholly to the local blood flow.

It has been noted that subjects with arthritis often complain of cold hands and feet and that the nails and finger tips may appear cyanotic or somewhat blanched. In the series of 700 civilians studied

3. Peirce, E. G., and Pemberton, Ralph: The Red Cell Count in Arthritis. *Arch. Int. Med.* **39**:421 (March) 1927. Cronter, C. Y., and Cajori, F. A.: The Red Cell Count in Arthritis: Second Paper, *Arch. Int. Med.* **39**:429 (March) 1927.

4. Pemberton, Ralph: Arthritis and Rheumatoid Conditions: Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

5. Lewis, T.: The Blood Vessels of the Human Skin, and Their Response, London, Shaw & Sons, 1927, p. 7.

5a. Pemberton (footnote 4, p. 75). Swaim, L. T., and Spear, L. M.: Boston M. & S. J. **197**:350, 1907.

6. Cecil, R. L.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry: XXXI. Observations on the Metabolism of Arthritis. *Arch. Int. Med.* **29**:583 (May) 1922.

6a. Pemberton (footnote 4, p. 101).

by E. G. Peirce and one of us (R. P.^{6b}), paresthesias of various kinds, suggestive of circulatory disturbance, were encountered with surprising frequency. It became important, therefore, to determine whether or not clinical impressions such as these could be substantiated by more nearly precise methods.

Studies were therefore undertaken on the surface temperature of arthritic subjects at the periphery (fingers, hands and forearms), the method described by Benedict being used; namely, the difference of electric potential developed in a thermocouple, on application to the part, and recorded by a galvanometer. Benedict and Parmenter⁷ noted that exposure to severe cold, with or without strenuous exercise, resulted in a lowering of the skin temperature, chiefly of the extremities. Talbot and his associates⁸ used this method in determinations of the surface temperatures of children, and Mudd and his collaborators⁹ observed a drop in the temperature of the nasal mucosal surface after chilling of the body surface.

It was further partly the object of the present studies to obtain evidence explanatory of the response of the arthritic subject to environmental changes due to the weather. It is well recognized that sufferers from arthritis experience exacerbations more or less coincident with such changes.

Human beings live at the bottom of an ocean of air in which movement, pressure, humidity, temperature and other factors are constantly varying. The influence of climate on persons and even on races is recognized in a wide sense of the word but there would be advantage in attaching precise figures to many current impressions regarding the weather and thus modifying or extending knowledge in this field, especially in relation to disease.

In a series of observations begun during the World War and conducted over several years among arthritic soldiers and civilians,^{9a} no fixed relationship was observed between exacerbations in arthritic processes and abrupt changes in temperature, humidity or barometric pressure. It was noted, however, that more or less contemporaneously with exacerbations there was a tendency for the barometer to fall and for the humidity to rise. Since the publication of these results, Rentschler, Vanzant and Rowntree¹⁰ reported "a positive relationship for

6b. Pemberton (footnote 4, p. 45).

7. Benedict, F. G., and Parmenter, H. S.: *Am. J. Physiol.* **87**:633, 1929.

8. Talbot, F. B.; Dalrymple, A. J., and Hendry, M. F.: *Skin and Temperatures in Normal Children*, *Am. J. Dis. Child* **30**:483 (Oct.) 1925.

9. Mudd, S.; Goldman, A., and Grant, S. B.: *J. Exper. Med.* **34**:11, 1921.

9a. Pemberton (footnote 4, p. 328).

10. Rentschler, E. B.; Vanzant, F. R., and Rowntree, L. G.: *Arthritic Pain in Relation to Changes in Weather*, *J. A. M. A.* **92**:1995 (June 15) 1929.

72 per cent of the time between the curve of pain and that of barometric pressure," viz., as the barometric pressure fell, the pain increased and as the barometric pressure rose, the pain decreased in a group of 367 patients. It was decided, therefore, to include in the present observations a study of the response of the arthritic patient to changes in the environment, cold being used as one of the factors concerned in meteorologic changes at large.

METHOD

The apparatus employed was that described by Bazett and McGlone¹¹ for the determination of surface temperatures, constantan wire and iron wire being used as thermo-elements. The apparatus was calibrated each day. Before the temperature of a given point was taken, the surface thermocouple was warmed by being placed in contact with a nearby point. The points chosen for the determination of the surface temperature were: the palm of the hand between the middle and fourth fingers; the back of the hand at (1) the base of the nail of the middle finger; (2) the midphalangeal joint of the middle finger; (3) the knuckle of the middle finger, and (4) the wrist. When the subject entered the laboratory, he was placed in the room where the study was to be carried out and was allowed to remain until comfortably warm, by which time he or she had presumably approached an equilibrium. This usually required half an hour, or slightly longer. The sleeve of the arm to be studied had meanwhile been rolled to the elbow, all constriction being avoided. The skin temperatures of the aforementioned points were taken every two minutes until the temperature of each point was approximately constant. The attempt was made to obtain readings indicative of a relative constancy of temperature of the hand as a whole in relation to the surrounding medium. Constancy of temperature of each point was not always possible, for the temperature of any given point changes normally. Occasionally, the difference between the successive final readings at any given point was greater than 1 C. It is to be noted, however, that Talbot and his associates⁸ found comparable variations in the skin temperature of a group of children covered by a double layer of blankets.

After the foregoing preparation, the subject was then covered with a coat, blankets and a hat. The hand and arm which were being used for study were exposed to the air and the subject was placed in a cold storage room for ten minutes. At the end of that time he was taken out of the cold room, unwrapped and brought back into the aforementioned warm room, as quickly as possible. Skin temperatures were taken at the following intervals: one, three, five, seven, ten, thirteen, sixteen, twenty and twenty-five minutes or two, four, six, eight, ten, thirteen, sixteen, twenty and twenty-five minutes, with occasional exceptions. Few of the experiments were continued beyond the twenty-five minute interval. Some cases were followed in the ward, where the pulse, respiration and systemic temperature could be observed over long periods. These cases showed no deviations from the normal to account for the experimental results obtained. The experiments have been divided into the two following groups:

GROUP 1.—This group consisted of sixteen arthritic and eleven normal subjects. The room in which the subjects were studied contained a door, a ventilator and one window, and the subjects were so placed in this room that drafts were avoided as much as possible. The temperature of the room ranged between 26

11. Bazett, H. C., and McGlone, B.: *J. Lab. & Clin. Med.* 12:913 (June) 1927.

and 26.8 C. (78.8 and 80.2 F.). It usually changed not more than 0.8 C. during any observation. The temperature of the cold room, which was controlled by a thermostat, averaged 7.2 C. (45 F.) plus or minus 1 C. One normal subject was studied on the same day as that on which one or more arthritic subjects were studied, the conditions being kept as similar as possible. (There was one exception to this statement: Two arthritic subjects were studied on one day and their normal control was run through on the following day.) The arthritic and the normal control subjects were equally well wrapped in the cold room.

GROUP 2.—Group 2 included twenty-six arthritic and ten normal subjects. In the studies in group 2, one experiment, on a normal subject, was carried out in a main laboratory room, and six experiments, one on an arthritic subject and five on normal subjects, were carried out in another of the laboratory rooms. These studies were carried out before the importance of drafts was fully appreciated, and each of these rooms was drafty. To avoid this error the subsequent twenty-four subjects from group 2, including twenty-two arthritic and two normal subjects, were studied in the dark room, the circuitous entrance of which effectively cut off all drafts. This room, however, had the disadvantage of becoming humid and warm before the end of the experiment. Experience finally showed that the experiments could be best carried out in the room described under group 1. Three arthritic and two normal subjects of group 2 were studied in here. Except for the last five experiments the attempt was not made to standardize the room temperature, which averaged from 25.5 to 26.1 C. (77.9 to 79 F.). In group 2, a normal control was not run through on the same day as was an arthritic subject, nor were the normal subjects as warmly wrapped in the cold room as the arthritic subjects. The cold room temperature, which was controlled by a thermostat, averaged 6.7 C. (44 F.) plus or minus 1.5 C. In one experiment, the subject was placed outdoors for ten minutes instead of in the cold room, the outdoor temperature being 9.4 C. (49 F.).

RESULTS

Studies of the surface temperature at the base of the nail of the middle finger gave the following results:

In Group 1.—(a) The initial temperature of 75 per cent of the arthritic subjects was lower than that of the average normal subject.

The initial temperature of 44 per cent of the arthritic subjects was lower than that of the lowest normal subject, which was 32.1 C.

The average initial temperature of the arthritic subjects was 31.2 C. The average initial temperature of the normal subjects was 33.7 C.

(b) After ten minutes in the cold room, 100 per cent of the arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 81 per cent of the arthritic subjects showed a lesser drop in temperature than did any normal subject.

The average drop in temperature was 6.6 C. for the arthritic and 10.7 C. for the normal subjects.

(c) Fifty-six per cent of the arthritic subjects returned to the precold room level before the end of the experiment, as compared with 36 per cent of the normal subjects.

The average time of return of skin temperature to the previous level, within 0.1 C., was sixteen for the arthritic and nineteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the arthritic subjects should have returned to the precold room level in twelve instead of sixteen minutes.

The rate of return is only approximated, because graphs show that it is not a straight line function.

In Group 2.—(a) The initial temperature of 50 per cent of the arthritic subjects was lower than that of the average normal subject.

The initial temperature of 19 per cent of the arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the arthritic subjects was 31.9 C.; that of the normal subjects, 32.7 C.

(b) After ten minutes in the cold room, 69 per cent of the arthritic subjects showed a lesser drop in temperature than the average normal subject.

After ten minutes in the cold room, 31 per cent of the arthritic subjects showed a lesser drop in temperature than did any normal subject.

The average drop in temperature was 6.1 C. for the arthritic and 8.3 C. for the normal subjects.

(c) Sixty-five per cent of the arthritic subjects returned to the precold room level before the end of the experiment, as compared with 67 per cent of the normal subjects.

The average time of return was twelve for the arthritic and fifteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the arthritic subject should have returned to the initial temperature in eleven instead of twelve minutes.

The observations in group 2, the less accurately controlled group, are in consonance with those in group 1, although the departures from normal are not so great.

Studies of the skin temperature of the midphalangeal joint, of the knuckle, and of the wrist for both groups showed:

(a) The difference between the initial temperature of the arthritic and normal subjects was less marked at these points.

(b) The drop in temperature of the arthritic and the normal subjects after ten minutes' exposure in the cold room, was also less marked at these points.

(c) The difference between the drop in temperature of the arthritic and of the normal subjects, after ten minutes' exposure in the cold room, was less marked at these sites.

(d) As the hand and wrist were ascended, the initial temperature of the arthritic approached that of the normal subject, and the drop in temperature of the arthritic subject, after ten minutes' exposure in the cold room, approached that of the normal subject.

The emphasis placed on the two types of arthritis, namely, atrophic and hypertrophic, which are receiving increasing recognition, makes it desirable to determine the degree to which, if at all, these observations varied in the two types mentioned.

Most of the cases in the present study were of the atrophic variety. In view of the relatively small number of hypertrophic cases in this series, all cases in group 1 and group 2 which could be differentiated into types are considered together.

Atrophic Arthritic Subjects.—Twenty-eight observations were made on twenty-four subjects.

(a) The initial temperature of 54 per cent of the atrophic arthritic subjects was lower than that of the average normal subject.

The initial temperature of 25 per cent of atrophic arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the atrophic arthritic subjects was 31.7 C. The average initial temperature of the normal subjects was 33.3 C.

(b) After ten minutes' exposure in the cold room, 82 per cent of the atrophic arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 21 per cent of the atrophic arthritic subjects showed a lesser drop in temperature than any normal subject.

The average drop in temperature was 6.6 C. for the atrophic arthritic and 9.6 C. for the normal subjects.

(c) Sixty-four per cent of the atrophic arthritic subjects returned to the precold room level before the end of the experiment, as compared with 50 per cent of the normal subjects.

The average time of return was fifteen for the atrophic arthritic and sixteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the atrophic arthritic subject should have returned to the initial temperature in eleven instead of fifteen minutes.

Hypertrophic Arthritic Subjects.—Nine observations were made on seven cases.

(a) The initial temperature of 78 per cent of the hypertrophic arthritic subjects was lower than that of the average normal subject.

The initial temperature of 22 per cent of the hypertrophic arthritic subjects was lower than that of the lowest normal subject, which was 30.2 C.

The average initial temperature of the hypertrophic arthritic subjects was 31.6 C.; that of the normal subjects was 33.3 C.

(b) After ten minutes in the cold room, 100 per cent of the hypertrophic arthritic subjects showed a lesser drop in temperature than did the average normal subject.

After ten minutes in the cold room, 44 per cent of the hypertrophic arthritic subjects showed less of a drop of temperature than did any normal subject.

The average drop in temperature was 4.8 C. for the hypertrophic arthritic and 9.6 C. for the normal subjects.

(c) Sixty-seven per cent of the hypertrophic arthritic subjects returned to the precold room level before the end of the experiment, as compared with 50 per cent of the normal subjects.

The average time of return was nine for the hypertrophic arthritic and sixteen minutes for the normal subjects.

Calculated on the basis of the rate of return for normal subjects, the hypertrophic arthritic subject should have returned to the initial temperature in eight instead of 9 minutes.

Indefinite Arthritic Subjects.—Five observations on three indefinite cases of arthritis showed closely comparable changes of the same order as were observed in arthritic subjects as a whole.

Contrary to what might have been expected, since atrophic arthritis is regarded as the more acute condition, these observations appear to indicate that the hypertrophic type shows as great departures from normal as does the atrophic type.

The skin temperature of finger joints, the seat of a frankly inflammatory process, is higher than the skin temperature of the corresponding noninflamed joint of another finger. For example, the initial temperature of an acutely involved joint, in the case of Mrs. Lws., showing atrophic arthritis, was 0.4 C. higher than that of the uninvolved joint; the temperature drop of the involved joint was 3.2 C. less than that of the uninvolved, and the return of the involved joint parallel that of the uninvolved finger of the arthritic subject.

It is to be noted that the lesser drop of the arthritic subjects as compared with that of the normal subjects is referable not alone to having started at a lower level. This is well illustrated by the construction of average curves for the normal and the arthritic subjects

(chart). Such curves show that, although the arthritic subject starts about 2 C. lower, he reaches a low point 1.5 C. higher than the low point of the normal subject.

TABLE 1.—*Study of Temperature of Base of Finger-Nail*

Subjects	Number of Observations	Average Initial Temperature, Centigrade	Per Cent of Arthritic Subjects Below Average Normal Subject	Per Cent of Arthritic Subjects Below Lowest Normal Subject	Average Temperature Drop, Centigrade	Per Cent of Arthritic Subjects with Less Drop Than Average Normal Subject	Per Cent of Arthritic Subjects with Less Drop Than Any Normal Subject	Per Cent of Subjects Showing Return to Initial Temperature	Average Time of Return, Minutes	Rate of Return in Degrees per Min.
Group 1										
Arthritic.....	16	31.2	75	44	6.6	100	81	56	16	0.41
Normal.....	11	33.7			10.7			36	19	0.56
Group 2										
Arthritic.....	26	31.9	50	19	6.1	69	31	65	12	0.51
Normal.....	10	32.7			8.3			67*	15	0.55
Whole Group										
Atrophic arthritic.....	28	31.7	54	25	6.6	82	21	64	15	0.44
Hypertrophic arthritic.....	9	31.6	78	22	4.8	100	44	67	9	0.53
Indefinite arthritic.....	5	31.1	80	20	7.2	100	20	40	13	0.55
Arthritic.....	42	31.6	62	24	6.3	88	26	62	13	0.48
Normal.....	21	33.3			9.6			50†	16	0.60

* Base on nine cases.

† Based on twenty cases.

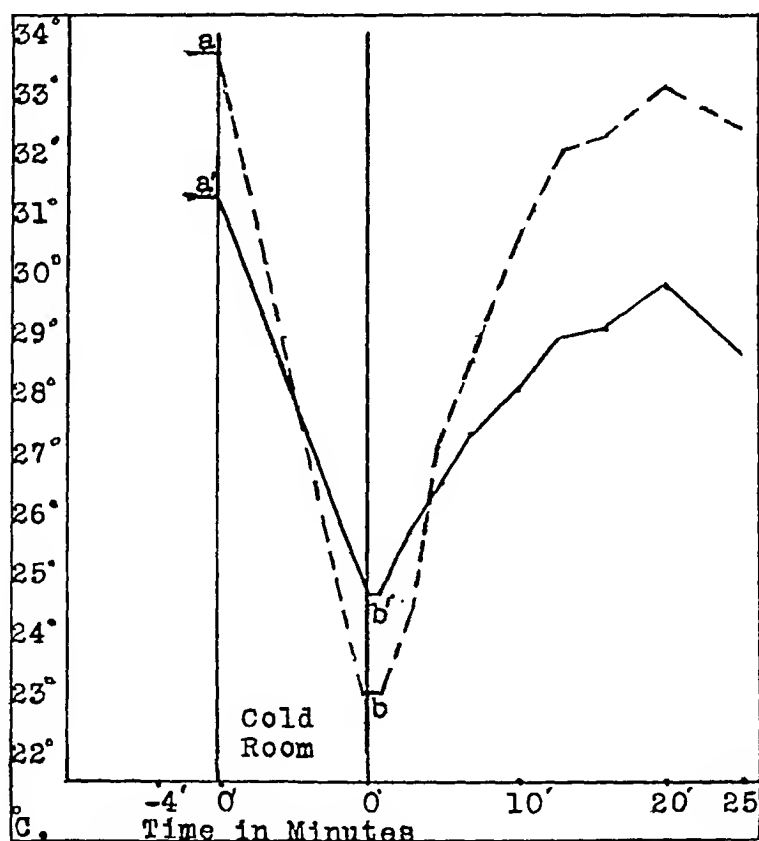
TABLE 2.—*Other Points of the Investigation*

Subjects	Midphalangeal Joint			Knuckle			Wrist			Palm		
	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade	No. of Observations	Average Initial Temperature, Centigrade	Average Temperature Drop, Centigrade
Group 1												
Arthritic	16	31.5	5.2	16	31.5	3.8	16	31.9	3.4	16	32.2	3.7
Normal..	11	33.3	7.9	11	32.8	5.1	11	32.9	4.8	11	33.6	5.2
Group 2												
Arthritic	18	32.5	4.6	18	32.6	3.6	20	32.7	3.2	17	32.9	3.3
Normal..	4	33.2	6.7	4	32.7	5.1	4	32.7	4.4	4	33.5	4.2
Whole Group												
Arthritic	34	32.1	4.9	34	32.0	3.7	36	32.4	3.3	33	32.5	3.5
Normal..	15	33.3	7.6	15	32.8	5.1	15	32.9	4.7	15	33.5	4.9

The fact that the arthritic subject has colder hands than the normal subject, under comparable conditions, was noticed while another group of experiments was being carried out. While preparing the subject for direct capillary observations, it was found that it was more difficult to warm an arthritic subject to the minimum of 32 C. at the base of

the nail, as determined by the thermocouple, and to keep him warm, than was the case with normal subjects. In the winter especially it was frequently necessary to apply a hot water bottle to the hand to bring the temperature of the part to this level. . In several cases the arthritic hand, warmed to 32 C., would not stay warm at room temperature long enough for a capillary observation to be made.

Corroboration of the explanation given at the outset for the cold hands of the arthritic subject was obtained by Dr. E. G. Peirce while the capillaries at the bases of the nail were being directly observed. The



The initial surface temperatures at the periphery of normal and arthritic patients and the response to exposure to cold. The broken line represents the normal temperature curve; the solid line, the arthritic temperature curve; *a*, normal initial temperature; *a'*, arthritic initial temperature; *b*, normal temperature after ten minutes' exposure; *b'*, arthritic temperature after ten minutes' exposure.

capillary field ² of the average arthritic subject contained less blood and was lighter in color than that of the average normal field. This may have been due to the fact that there were fewer capillaries open or to a difference in the size of the capillaries. Under approximately the same conditions of temperature, the blood flow in the capillary field of the average arthritic subject was not so rapid as that in a normal field; it was not so steady, and there were more breaks in the column of blood as it flowed through the capillaries. This arthritic capillary picture was made to

approach the normal by raising the skin temperature at the base of the nail several degrees Centigrade. A detailed report of this work is now in progress.

In keeping with these thermometric observations on forty-two arthritic and twenty-one normal subjects is the observation of Rowntree and Adson¹² on a patient with severe arthritis in whom the operations of bilateral lumbar and cervicothoracic ganglionectomy were followed by an apparent change of color and rise of temperature both in the upper and the lower limbs, which had previously been cold and clammy.

SUMMARY

The observations recorded reveal that, under adequately controlled conditions of study, 75 per cent of arthritic subjects maintain at the periphery, (the base of the nail), a temperature lower than that of normal persons under comparable circumstances. They also show that under conditions of exposure to cold, the temperature of the arthritic subject at the periphery drops less than does that of normal subjects, partly, but not wholly, because of starting at a lower level. The return of the peripheral temperature of the arthritic subject to the precold room level appears to be relatively slower than that of normal subjects. It is difficult to explain these differences between arthritic and normal subjects on a basis other than that of diminution in, or at least disturbance of, the capillary blood flow.

These observations, further, throw light on the mechanism operative in the exacerbations experienced by arthritic subjects during fluctuations in the weather. They imply that the capillary bed, and presumably its control by the vasomotor system, is less labile in respect to adaptations demanded of it by changes in the environment. Inadequacy of response of this nature doubtless expresses itself in terms of further disturbances in the physiology of the part concerned. In the already handicapped tissues of the arthritic subject, this may mean added dysfunction and pain.

Finally, these observations lend further support to the evidence already advanced that an important part of the phenomena of arthritis and the rheumatoid syndrome is referable to disturbances in the peripheral blood flow.

12. Rowntree, L. G., and Adson, A. W.: Polyarthritis: Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisectomy, *J. A. M. A.* **93**:179 (July 20) 1929.

Book Reviews

A TEXTBOOK OF MEDICINE. By Various Authors. Edited by J. J. CONYBEARE, M.C., M.D. (OXON.), F.R.C.P. Pp. 947. New York: William Wood & Company, 1929

The contributors, in addition to J. J. Conybeare, are: W. H. Craib, Geoffrey B. Dowling, E. H. R. Harries, Arthur Maitland-Jones, Vernon E. Lloyd, Hugh Maclean, Geoffrey Marshall, Trevor Owen and F. M. R. Walshe. This list of names gives assurance of itself that the book will be a valuable one.

The book contains a compact, concise, clearcut description of every disease commonly grouped under the heading of general medicine. It has in addition sections devoted to neurology and dermatology, including all but the rare conditions occurring in these fields. So it is not only an ideal volume for teaching purposes, but a convenient reference for physicians in any specialty. The intern or young general practitioner would find it particularly useful.

It is a readable work from the point of view of style. One even finds an occasional stroke of humor—a thing appearing all too rarely in medical literature—such as the statement that prohibition in the United States has brought to light the toxic properties of methyl alcohol, or the description of the gambler with gout who made chalk marks on the table with the tophi on his knuckles.

One or two features may detract from the usefulness of the book in this country. Most of the medications are those of the British Pharmacopoea, and while the American equivalent is usually apparent, the change might be somewhat confusing to students.

The discussion of thyrotoxicosis is open to criticism in the light of experience with that disease in the Middle West. Conybeare makes a sharp distinction between the Grave hyperplastic type and the toxic adenomatous form, and adds that iodine is of no avail in the treatment for the latter. The reader is given no warning that he will meet with many patients having some of the characteristics of both groups. The author says that operation as a rule should not be considered before six months of medical treatment; roentgen treatment, he leads one to believe, should be abandoned. But of course this disease is more common and severe in this country than in England; so the treatment may vary in the two localities.

The rest of the book is sound in every respect. The treatment for syphilis is systematized and detailed in a thorough fashion. The section on diabetes is particularly admirable. It is the equivalent of a handbook on the subject, with diet tables, sample diets and a regimen that uses the best parts of the several schools of treatment without the extremes of any.

The treatment for peptic ulcer does not resemble that of Sippy or Mills, and the drugs are not those in common use in America, but no doubt they accomplish the same results.

The subject of heart disease is well presented. The principles of the electrocardiograph are clearly stated and described in such a way as to be of great assistance to the beginner.

The editor has eminently succeeded in his attempt, as stated in the Preface, "to provide within as small a compass as possible the essentials of medicine, without, however, producing anything in the nature of a synopsis."

LEHRBUCH DES STOFFWECHSELS UND DER STOFFWECHSELKRANKHEITEN. By DR. MED. ET PHIL. S. J. THANNHAUSER. Price, 56.80 marks. Munich: J. F. Bergmann, 1929.

Thannhauser's book presents a discussion of diseases in which biochemical processes are prominent, by a clinician trained and experienced in biochemistry,

who has himself been an industrious and successful investigator in the field of metabolic disorders. The result is an unusually successful balancing of the clinical and the laboratory points of view, so that each chapter is equally full of interest and suggestion for both the clinician and the laboratory worker. It is based on a series of lectures by the author, who is director of the medical clinic in Düsseldorf, and therefore possesses the advantage of readability usual in published lectures. Such a work cannot exhibit the complete familiarity with all fields expected in books compiled by several specialists, but it does possess the advantage of presenting a balancing and analysis of the specialists' contributions by a qualified physician competently utilizing in the clinic the most recent contributions of the biochemical laboratory. The result is a most useful volume that can be cordially recommended to every progressive physician and biochemist. Excellent selection has been made from the vast literature available, and the author is familiar with more of the world's literature than is always the case with his compatriots. Diabetes receives the most extended discussion, occupying 215 of the 715 pages of text, and it is a well balanced presentation. Purine metabolism and gout are particularly well discussed, the author adhering to the view that there are two sorts of gout, one depending on a selective primary deficiency of the capacity of the kidney to eliminate uric acid, this being unaccompanied by observable anatomic alterations or other defects of the kidney; the other is merely a stage of progressive chronic nephritis in which the retention of uric acid is only a part of the general functional deficiency. Fat metabolism, with its abnormal manifestations of obesity and emaciation, is well covered. Protein metabolism is presented in conventional manner, and the pigmentary metabolism is thoroughly reviewed. There are also sections on total metabolism, and on mineral and water metabolism, including a discussion on neutrality regulation which will probably impress American readers as perhaps less adequate than some of the other presentations. All in all, this "Lehrbuch" offers an excellent middle-power view of the field of metabolic diseases with good perspective and little distortion.

UEBER ORGANHORMONE UND ORGANTHERAPIE. By GEH.-RAT PROF. DR. AUGUST BIER, DR. W. FEHLOW, DR. A. GEHRKE, DR. U. LUETKENS and PRIVAT-DOZENT DR. A. ZIMMER. Price, 4.50 marks. Pp. 91. Munich: J. F. Lehmanns, 1929.

This is not a monograph on hormone therapy, but contains four brief reports on some of the nonsurgical therapies followed in the surgical clinic of Dr. Bier. The first paper is a general discussion, with an account of the experience with intravenous injections of foreign blood by Dr. Bier. An item of great historical interest is referred to, namely, that the ancient Arab and Persian physicians treated patients with severe anemias (we are not told how successfully) by feeding them with liver. If this is correct, the recent liver therapy of anemia is a rediscovery. Dr. Luetkens and Dr. Gehrke report on treatment for diseases of the liver and gallbladder with crude extracts of gallbladders and liver ("Choloton schwach," and "Choloton stark"). Dr. Gehrke states that for many years he has treated patients with tabes, progressive paralysis, multiple sclerosis, etc., by feeding them animal brain substance ("Promonta"). Finally, there is a short account by Dr. Zimmer and Dr. Fehlow on the treatment of patients with toxic goiter by the intravenous injection of foreign blood. They claim that therapy (essentially foreign protein) increases appetite, reduces nervousness and insomnia and increases body weight, by "its deep influence on restoring the harmony of function" (p. 88).

Apart from the distinct foreign protein therapy, a field in which experimentation is still warranted, if one takes steps to control the usual "post hoc" errors, this twentieth century excursion of surgeons into internal medicine reveals little or no advance on the "tiger bone therapy" of the ancients.

LYMPHOMA

A STUDY OF ONE HUNDRED AND FIFTY CASES *

C. W. BALDRIDGE, M.D.

AND

C. D. AWE, M.D.

IOWA CITY

The recent medical literature contains many reports dealing with the unusual manifestations¹ of that disease which is characterized by progressive enlargement of the fixed lymphatic tissue and a fatal termination. It has no doubt occurred to most clinicians who are interested in this subject that the unusual manifestations are being reported without any definite idea as to what comprises the usual. For this reason, we feel that the information derived from the study of 150 consecutive cases in the University Hospital might be worth recording. The data obtained in our study will be presented in tabular form, and the discussion of obvious facts will be avoided.

No generally accepted terminology for the conditions under consideration exists. One finds clinical classifications and classifications based on pathologic histology as well as attempts to combine the two. Etiology remains a matter of opinion,² and pathologic concepts are often almost lost in a maze of names. We have heard the term "malignant lymphoma" given two different meanings by members of the same hospital staff. Because of the existing confusion, every one discussing the subject must either explain his terminology at length or accept the risk of being misunderstood.

We do not wish to discuss terminology or to defend that which we shall use in this communication. We shall use the terminology with which we are familiar and supplement each term with a few common synonyms when such exist.

Lymphoma (lymphoblastoma) (malignant lymphoma)

1. Sclerosing type (Hodgkin's disease) (lymphogranuloma)

2. Endothelial type (lympho-epithelioma)

3. Lymphoblastic type (lymphosarcoma)

4. Lymphocytic type

With leukemia (lymphatic leukemia) (lymphocytic leukemia)

Without leukemia (pseudoleukemia) (aleukemic leukemia)

* Submitted for publication, June 18, 1929.

* From the Department of Internal Medicine, University of Iowa.

1. Barron, M.: Unique Features of Hodgkin's Disease (Lymphogranulomatosis) with Report of Three Unusual Cases and a Summary of Twenty-Four Cases Studied at Necropsy, *Arch. Path.* 2:659 (Nov.) 1926. Holmes, G. W.: Unusual Manifestations of Lymphoblastoma, *Am. J. Roentgenol.* 16:107, 1926.

2. Simonds, J. P.: Hodgkin's Disease, *Arch. Path.* 1:394 (March) 1926.

Table 1 gives the number of cases falling into each group, together with the number of biopsies and necropsies.

Microscopic sections from thirty-nine complete and five partial necropsies and sixty-nine biopsies were restudied for this communication. The division of cases into the four principal types has been based on pathologic changes, except in twenty-five of the cases of lymphatic leukemia. Blood manifestations characteristic of lymphatic leukemia are so uniformly associated with the lymphocytic type of histologic change that we have accepted such manifestations in lieu of histologic study of lymph nodes in these twenty-five cases.

In situ, lymphomatous nodes have certain definite characteristics. They are usually firm, smooth, freely movable and not tender. The nodes vary in consistency, those in the sclerosing and endothelial types being hardest, but even these nodes are not as hard as those in metastatic carcinoma. The smooth surface and uniform density of lymphomatous nodes are in contrast with the irregular masses of scar tissue, fibrosed

TABLE 1.—*Types of Lymphoma*

	Cases	Biopsies	Necropsies	Cases Studied Histologically
Sclerosing type.....	46	36	15	46
Endothelial type.....	2	3	1	2
Lymphoblastic type.....	19	15	5	19
Lymphocytic type with leukemia.....	55	13	19	30
Lymphocytic type without leukemia.....	14	11	4	14
Unclassified*.....	14	0	0	0
Total.....	150	78	44	111

* Neither biopsy nor necropsy was done and blood manifestations were not those of leukemia.

fat and small lymph nodes often felt in the normal axilla. The expansive growth without periadenitis makes the early nodes of all types of lymphoma freely movable, contrasting again with the anchored nodes of old inflammation. Tuberculous lymph nodes are apt to be linked together in a chain by the thickened lymphatics which connect them. Tuberculous cervical lymph nodes are often freely movable from side to side, but movement up or down causes distinct tension on neighboring nodes. Tenderness, such as is characteristic of the lymph nodes in glandular fever and in other acute infectious conditions, is not seen in lymphoma.

The gross appearance of lymphomatous nodes removed at biopsy is often diagnostic. In addition to the enlargement, the hilum is pressed out, the capsule is tight, and the density is often increased. On section, the appearance varies in the different types. The appearance of the sclerosing type will depend on the amount of fibrosis and necrosis; the endothelial type may suggest carcinoma because of a light gray granular appearance; and the lymphoblastic and lymphocytic types show a uniform cut surface which is obviously cellular.

The sclerosing type with its fibrosis, giant cells and usually eosinophils and necrotic areas is quite easily recognized histologically, though it is possible to find rather marked quantitative variations in its elements (fig. 1). The endothelial type, which is apparently uncommon, contains areas of irregularly shaped cells with vesicular nuclei and abundant, poorly staining cytoplasm. In some of the nodes from one of our cases,

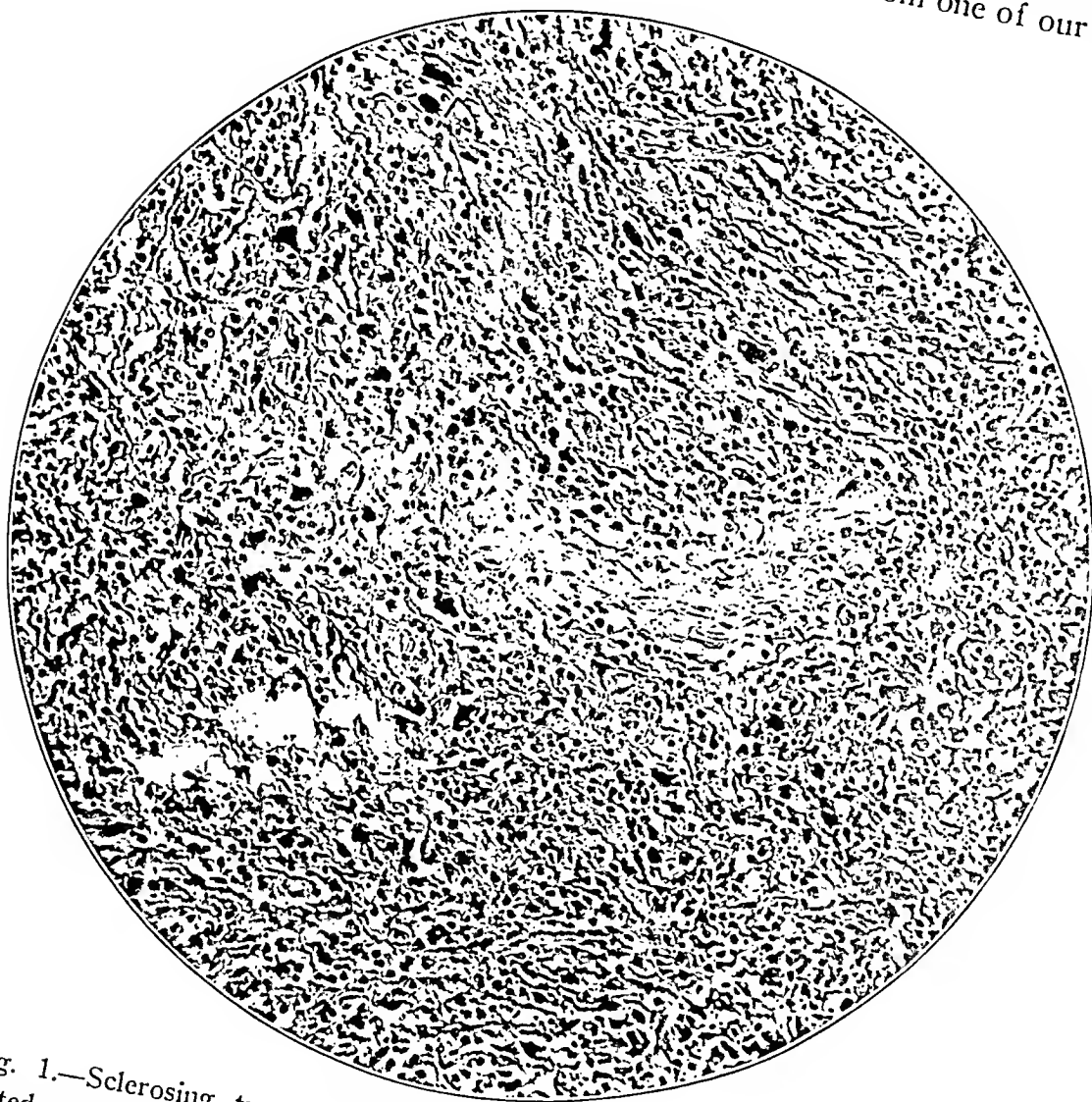


Fig. 1.—Sclerosing type of lymphoma. Numerous giant cells, both mononucleated and multinucleated and diffuse fibrosis are the outstanding features. This section also showed great numbers of eosinophils and a few small areas of necrosis. In long-standing cases, the fibrosis is usually in coarse bands.

the pathologic change was not unlike that seen in metastatic carcinoma (figs. 2 and 3). Ewing³ and others feel that the syncytial cells are epithelial rather than endothelial. Sections of nodes from the lympho-

3. Ewing, James: Lymphoepithelioma, *Am. J. Path.* 5:99, 1929.

cytic type give the appearance of a sac full of cells. The lymphoblastic type is quite similar, except that the cells are less uniform. In both these types the growth, which is expansive, obliterates the hilum and peripheral sinus, thus distorting the architecture beyond recognition.

In our series, invasion of the capsule and surrounding tissue has not been a reliable criterion in diagnosis of the lymphoblastic type (lympho-

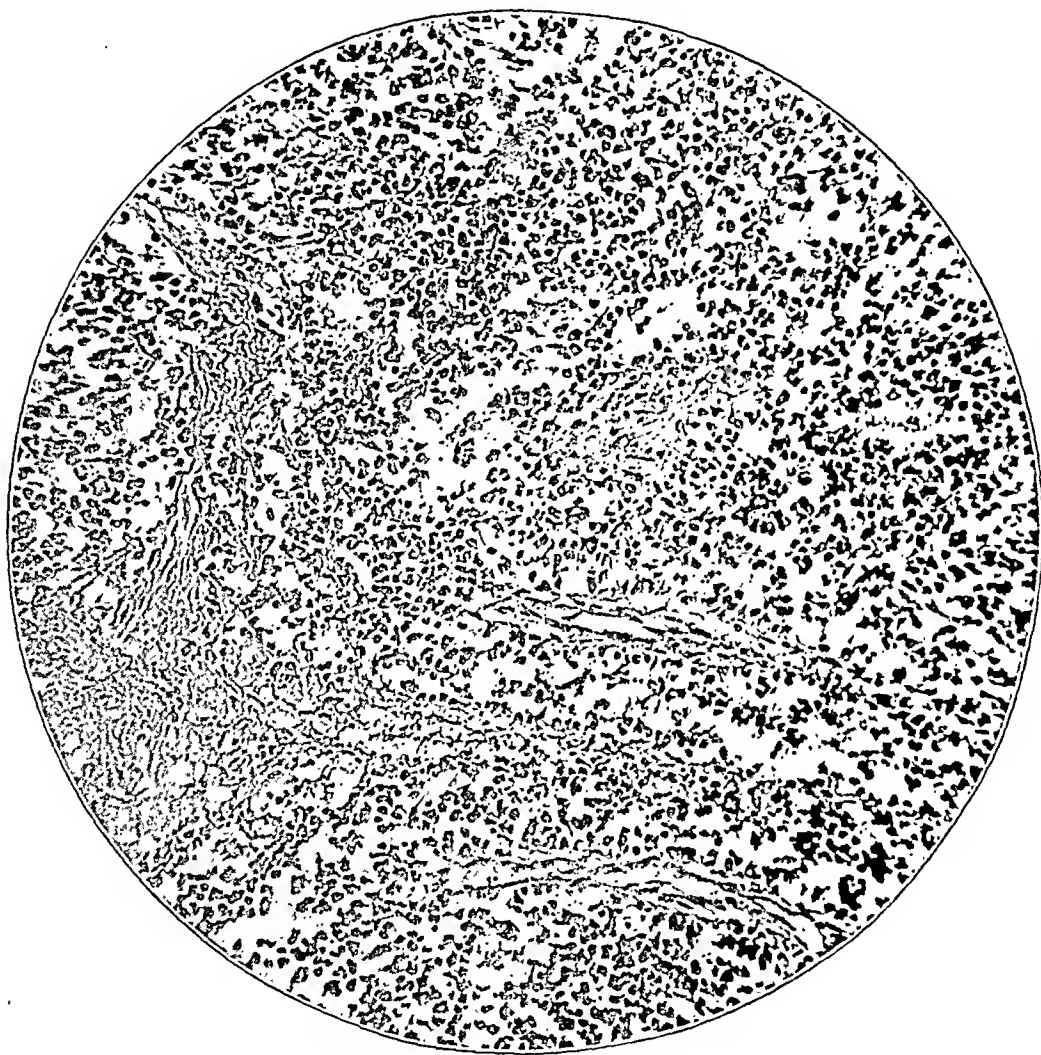


Fig. 2.—Endothelial type. The histologic picture seen in most of the enlarged nodes and in the metastatic lesions in the viscera. The cytoplasm of the cells is not well shown in the photograph.

sarcoma). The main difference between the lymphoblastic and lymphocytic types lies in the character of the cells making up the nodes (figs. 4 and 5). As one might expect, the cells are occasionally intermediate in character, and such borderline cases are so difficult of classification as to make this particular division seem artificial. The difficulty is most marked in lymphatic leukemia in childhood, in which the lymphoid cells

comprising the nodes are often larger and have slightly more cytoplasm than the cells seen in the lymphatic leukemia of adults. We have never discovered more than one type of pathologic change in the same patient.

Table 2 represents a study of the age and sex in the various types. The age at onset has been used in all instances. In the whole group of 150 cases, there were 101 males and 49 females, or a ratio of about 2:



Fig. 3.—Endothelial type, showing an area which has a striking resemblance to carcinoma in the appearance of cells, in their arrangement and in fibrous tissue reaction to their presence. Under higher magnifications, however, these groups of cells have the appearance of a syncytium, and relationship to the fibrous tissues is not the same as that between carcinoma cells and stroma. This section is from one of the nodes first enlarged which was removed about three months after irradiation. Two biopsies and a complete necropsy were done on this patient. No evidence of a primary carcinoma was found. The existence of an uninterrupted series of intermediate steps between the two extremes led to the conclusion that the sections pictured represent different phases of the same tumor.

In a larger series reported by Minot and Isaacs,⁴ males predominated 2.12:1. It will be noted that the females were in most types younger than the males. This feature was also mentioned by Minot and Isaacs. Lymphatic leukemia was especially common in old men and, strangely

TABLE 2.—*Age and Sex in Various Types*

	Cases	Average Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Sclerosing type.....	46	29								
Male.....	28	30	2	5	10	4	4	3
Female.....	18	25	1	1	12	2	..	1
Endothelial type.....	2	23								
Male.....	2	23	1	1
Female.....
Lymphoblastic type.....	19	45								
Male.....	12	44	..	2	3	..	1	1	5	..
Female.....	7	46	1	1	1	2	2	..
Lymphocytic type with leukemia.....	55	27								
Male.....	40	42	8	2	1	2	7	7	11	2
Female.....	15	24	7	2	..	1	2	2	1	..
Lymphocytic type without leukemia.....	14	40								
Male.....	11	44	1	3	3	2	2	..
Female.....	3	26	..	1	1	1
Total.....	136	..	20	13	28	16	18	18	21	2

TABLE 3.—*Duration of Disease*

	Cases	Number Followed to Death	Average Duration in Years	Longest Duration in Years	Shortest Duration in Years	Sex	Cases	Average Duration in Years
Sclerosing type.....	46	27	2.15	9	0.16	M F	13 14	2.24 2.08
Endothelial type.....	2	1	3	M F	1 ..	3
Lymphoblastic type.....	19	12	1.24	5	0.16	M F	8 4	1.5 0.7
Lymphocytic type								
With leukemia								
Adult.....	35	21	3.17	9	0.25	M F	17 4	3.0 3.9
Child.....	29	16	0.43	0.8	0.08	M F	8 8	0.35 0.52
Without leukemia.....	14	7	2.19	11	0.25	M F	5 2	0.69 6.1

enough, there were only two instances of its occurrence in patients between the ages of 11 and 38, both men, one 19 and the other 21.

The duration of the illness (table 3), was estimated from the date of the discovery of enlarged nodes or the onset of definite symptoms. It will be observed that the (progression of lymphatic leukemia was relatively slow in the adult, whereas in the child it was rapidly fatal.) In general,

4. Minot, G. R., and Isaacs, R.: Lymphoblastoma (Malignant Lymphoma), J. A. M. A. 86:1185 (April 17) and 1265 (April 24) 1926.

the patients with sclerosing lymphoma lived longer than those with the lymphoblastic form.)

No attempt has been made to study the effect of roentgen treatment on the duration of this disease. In lymphatic leukemia in children, roentgen treatment seemed to have a detrimental effect and has been discontinued. Most of the adult patients have received this form of treatment,

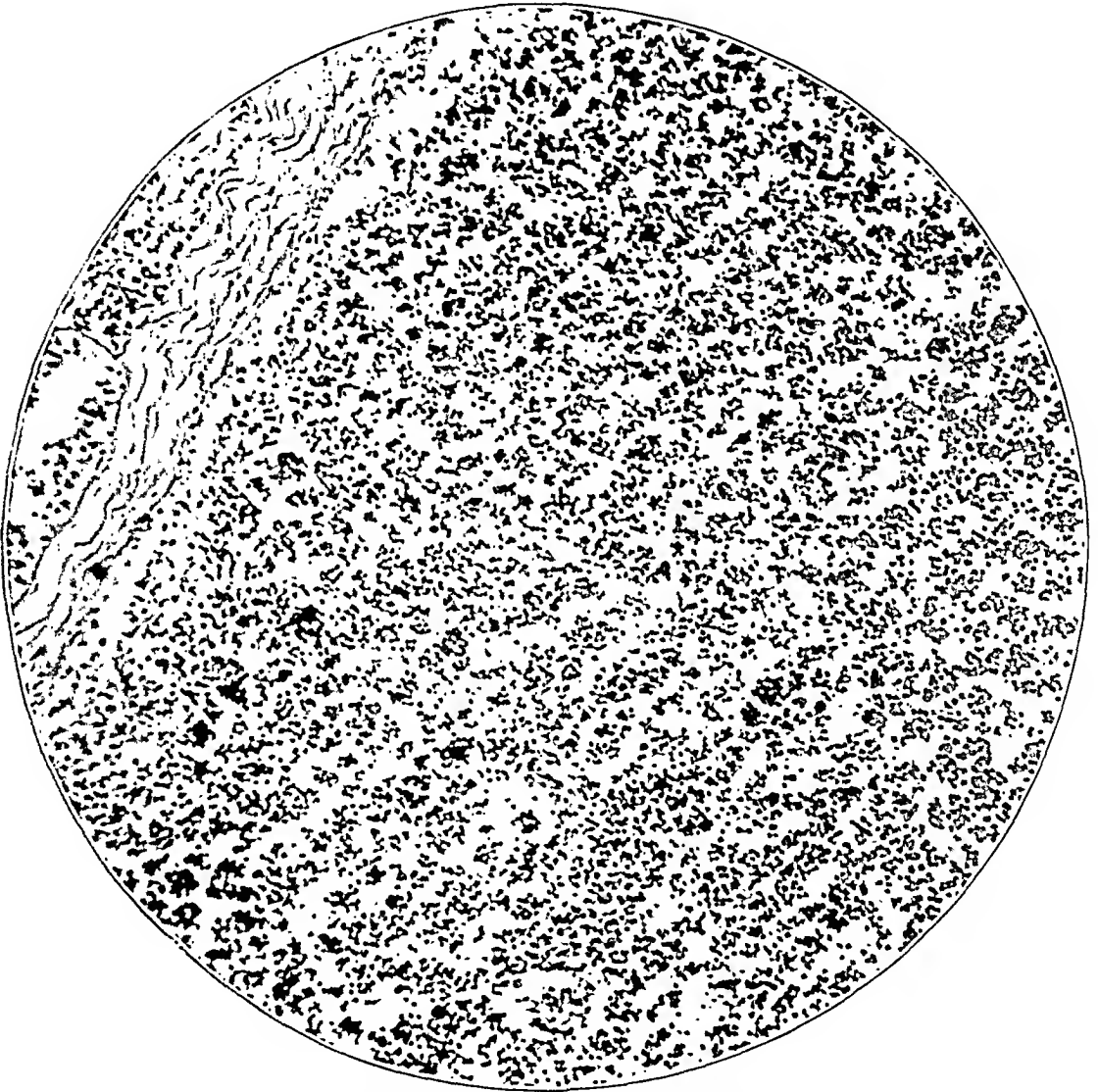


Fig. 4.—Lymphocytic type. The uniform small lymphocytes with little stroma, limited by the capsule of the node and a few trabeculae, give the appearance of a sac full of cells.

but so few have been given full doses at regular intervals, from beginning to end, that it seems unwise to draw general conclusions from a statistical study of this group. Aside from the possible influence on the length of life, roentgen treatment may be employed advantageously in certain cases to relieve pain, to prevent or delay the development of pleural effusion or ascites, or to improve the patient's general appearance.

An occasional instance of long duration may be noted in any form of lymphoma regardless of the type of treatment employed. Two patients with sclerosing lymphoma treated with the x-rays have remained quite comfortable for five and ten years, respectively. In three, in whom the cervical nodes were repeatedly removed surgically, the average duration was 6.6 years. In the latter group the enlarged nodes were

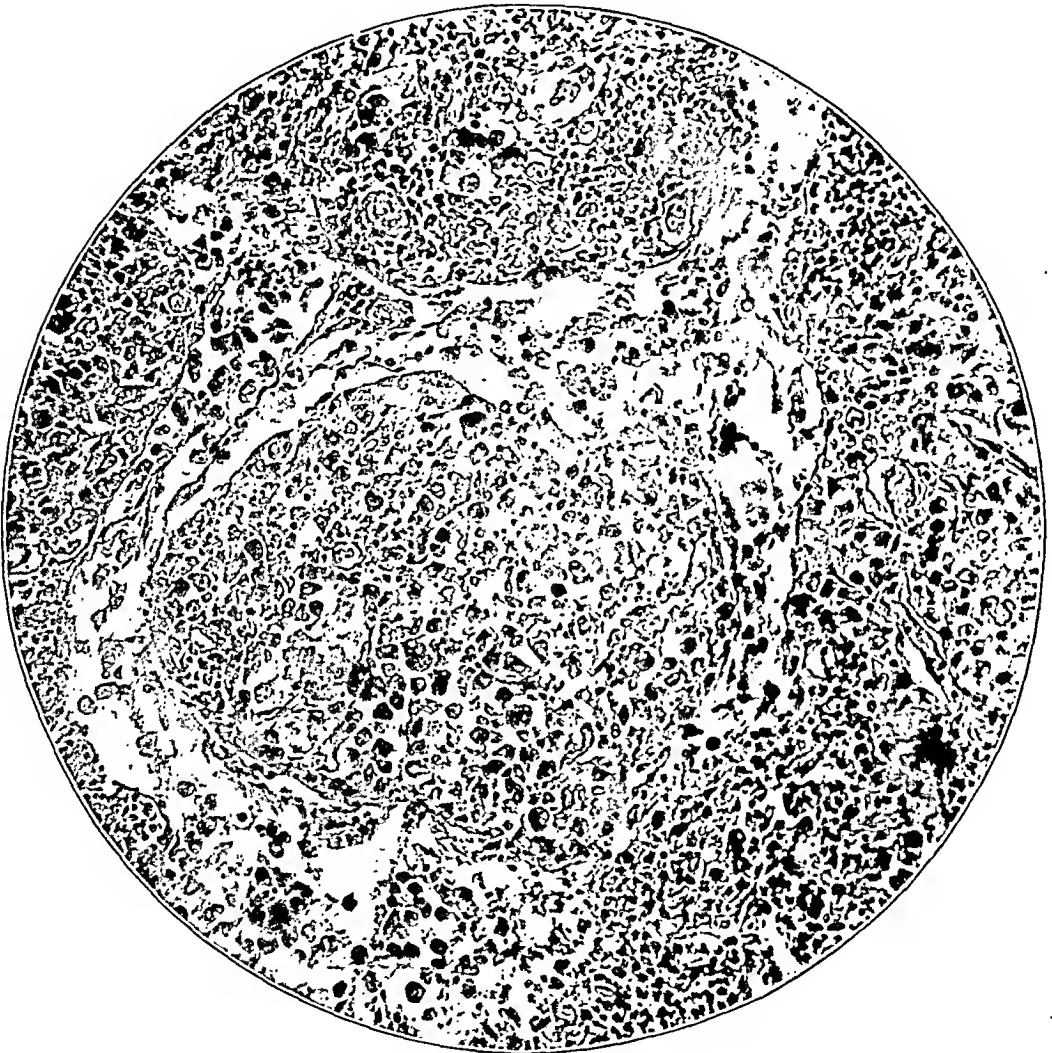


Fig. 5.—Lymphoblastic type. Cells which resemble those in a normal germinal center are scattered all through the node. There is more stroma than in the lymphocytic type but less than in the sclerosing type. Small lymphocytes are also present, and in places there are small pyknotic nuclei without recognizable cytoplasm.

confined for the most part to the neck, a form which may be very chronic. One patient with the lymphocytic type without leukemia lived eleven years and received no treatment for the first ten years of the illness.

Table 4 shows the incidence of involvement by lymph node groups as determined clinically, and table 5 is a similar tabulation from complete necropsy material.⁵ Table 6 indicates the first enlargement noted by the patient.

While the involvement of the superficial nodes is readily detected, it is well recognized that relatively gross enlargement of the mediastinal and abdominal nodes and of the spleen frequently escapes clinical obser-

TABLE 4.—*Lymph Node Groups Found Enlarged Clinically*

	Cases	Cervical	Axillary	Inguinal	Medias- tinal	Abdom- inal	Spleen
Sclerosing type.....	46	45	32	26	31	14	24
Endothelial type.....	2	2	2	..	1	1	..
Lymphoblastic type.....	19	19	15	13	11	12	10
Lymphocytic type							
With leukemia.....	55	52	50	48	33	31	46
Without leukemia.....	14	14	11	8	8	5	4
Unclassified.....	14	12	8	5	8	6	6
Totals.....	150	144	118	100	92	69	90

TABLE 5.—*Lymph Node Groups Found Enlarged at Necropsy*

	Cases	Cervical	Axillary	Inguinal	Medias- tinal	Abdom- inal	Spleen
Sclerosing type.....	13	13	12	10	13	12	11
Endothelial type.....	1	1	1	..	1
Lymphoblastic type.....	5	5	4	4	4	5	4
Lymphocytic type							
With leukemia.....	17	17	16	15	15	16	16
Without leukemia.....	3	3	3	3	2	3	0

TABLE 6.—*Lymph Node Groups First Enlarged*

	Cases	Cervi- cal	Axil- lary	Ingu- inal	Medias- tinal	Ab- dominal	Spleen	Tonsil	Skin	Not Noted*
Sclerosing type.....	46	35	2	2	2	2	2	1
Endothelial type.....	2	2
Lymphoblastic type...	10	14	..	2	1	2
Lymphocytic type										
With leukemia.....	55	32	..	4	1	3	6	..	1	8
Without leukemia....	14	8	..	2	2	1	1
Total.....	136	91	2	10	6	5	8	3	2	9

* No enlargement noted by patient before examination, and several groups of nodes were found to be involved at the first examination.

vation (tables 4 and 5). In lymphatic leukemia there is an enlargement of nearly all the lymph node groups early in the course of the disease. In the noncirculating types, however, the involvement may remain limited until the later stages, when it usually becomes generalized.

Information as to the nodes first involved must be largely taken from the history (table 6). Patients readily detect enlargement of the cer-

5. Desjardins, A. U., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. 81:925 (Sept. 15) 1923.

vical nodes; they are less apt to notice inguinal adenopathy and rarely discover an involvement in the axilla. Abdominal nodes are nearly always massive before the subject is aware of their presence, and an increase in the size of those of the mediastinum is not suspected until after the appearance of pressure symptoms.

Table 7 represents an attempt to divide the types of fever occurring in the lymphomas into Pel-Ebstein and other varieties. Only fever occurring during the period of hospitalization is recorded, and an effort has been made to exclude all extraneous fevers. Instances of continued or remittent fever of 102 F. or above, lasting from three to thirty days and recurring after a period of apyrexia, are considered indicative of the Pel-Ebstein type of the disease, providing no infection is demonstrable. The second group includes irregular remittent and intermittent fevers without obvious infection, although some were continuous with terminal fevers and may not have been entirely the result of lymphoma. It is to be noted that the Pel-Ebstein fever is most common in the

TABLE 7.—*Incidence of Fever*

	Cases	Pel-Ebstein Fever		Prolonged Fever, Not Pel-Ebstein		Slight or No Fever
		Number	Per Cent	Number	Per Cent	
Sclerosing type.....	46	18	39	8	17	20
Endothelial type.....	2	1	50	1
Lymphoblastic type.....	10	3	15	4	21	12
Lymphocytic type						
With leukemia.....	55	1	1.8	26	47	28
Without leukemia.....	14	1	7	4	28	9
Total.....	136	23	16	43	31	70

sclerosing type; however, it is by no means limited to this variety of lymphoma.

In one case, the fever was sufficiently remarkable to warrant special mention. The patient had four periods of fever, each lasting about thirty days, ranging between 102 and 105 F., and separated by periods of apyrexia of from nine to eleven days. During most of the course, the spleen was the only part of the lymphatic apparatus that was demonstrably enlarged. The size of the spleen varied greatly and paralleled the temperature curve. It gradually enlarged as the fever increased until the lower margin reached the level of the umbilicus, and during each interval of apyrexia it receded to the costal margin. Two weeks before death there was a moderate enlargement of the cervical nodes, and a mass was demonstrated in the mediastinum by roentgen examination. At necropsy the abdominal nodes were enlarged, and metastatic lesions were found in the liver. The histologic picture was that of the sclerosing type of lymphoma.

Tables 8, 9, 10, 11 and 12 contain a summary of the blood manifestations in the various types of lymphoma.

TABLE 8.—Leukocyte Count

		Below 5,000	5 to 10 Thousand	10 to 15 Thousand	15 to 20 Thousand	20 to 25 Thousand	25 to 30 Thousand	30 to 35 Thousand	35 to 50 Thousand	50 to 75 Thousand	75 to 100 Thousand	100 to 200 Thousand	200 to 300 Thousand	300 to 400 Thousand	400 to 500 Thousand	500 to 600 Thousand	600 to 700 Thousand
Sclerosing type.....	High	2	5	12	13	6	6	1	2	1
	Low	17	10	6	4	1
Endothelial type.....	High	1	..	2
	Low	3	9	5	2
Lymphoblastic type.....	High	0	12	1
	Low	2	4	2	4	5	1	3	7	7	3	3	3	4	..	1	1
Lymphocyte type With leukemia.....	High	3	9	4	1
	Low	3	7	3	1
Without leukemia.....	High
	Low

TABLE 9.—Variation in Leukocyte Counts

	Leukocyte Counts	
Sclerosing type.....	Highest	Lowest
Endothelial type.....	43,800	1,150
Lymphoblastic type.....	14,000	4,500
Lymphocyte type with leukemia.....	17,500	2,400
Lymphocyte type without leukemia.....	690,000	600
	15,800	4,000

TABLE 10.—Differential Blood Counts

	Neutrophils Polymorpho- nuclears			Basophils Eosinophils			Endothelials			Lymphocytes		
	Aver- age %	High %	Low %	Aver- age %	High %	Low %	Aver- age %	High %	Low %	Aver- age %	High %	Low %
Sclerosing type.....	72.8	89	47
Endothelial type.....	78	82	74	4.2	83	0	7.4	24	0	15.2	44	2
Lymphoblastic type.....	70	95	40	2	4	0	21	24	22	2	4	0
Lymphocyte type With leukemia.....	10	48	0	1	6	0	7	17	0	25	56	4
	66	83	37	0.1	1	0	0.4	10	0	89.5	100	53
Without leukemia.....	2	7	0	7	17	1	25	48	11

TABLE 11.—Erythrocyte Counts

		Millions										
		Below 1	1 to 1.5	1.5 to 2	2 to 2.5	2.5 to 3	3 to 3.5	3.5 to 4	4 to 4.5	4.5 to 5	Above 5	
Sclerosing type.....	High
	Low	..	2	1	6	7	2	10	14	8	5	..
Endothelial type.....	High
	Low	1	..	1	..	2
Lymphoblastic type.....	High
	Low	2	1	2	3	5	5	8
Lymphocyte type With leukemia.....	High	1	5	3	5	1	8	13	16	2
	Low	4	8	3	8	4	10	9	11	7	5	1
Without leukemia.....	High
	Low	2	3	2	3	6	1	1
		3	1	4	5	5	1	1

In table 8 the highest and lowest leukocyte values are recorded. It is to be noted that a leukocyte count of above 10,000 occurred in 63 per cent of the patients with the sclerosing type, in 37 per cent of those with the lymphoblastic type, in 89 per cent of the lymphocytic variety with leukemia, and in 35 per cent of those with lymphocytic lymphoma without leukemia. Counts of over 20,000 were obtained only in the sclerosing type and in lymphatic leukemia. (In our experience, the sclerosing type of lymphoma is the most frequent cause for a nonleukemic leukocytosis of 20,000 per cubic millimeter, or above, in an afebrile patient.) The leukocytosis of sclerosing lymphoma is likely to vary greatly from day to day. In 14 per cent of our patients with lymphatic leukemia the leukocyte count was never found to be above 15,000 per cubic millimeter. Leukocyte counts below 5,000 were fairly common in all types of lymphoma.⁶ Our experience indicates that a pronounced leukopenia in lymphatic leukemia is a much more definite contraindication to roentgen therapy than a similar count in the noncirculating varieties.

TABLE 12.—*Terminal Anemia*

Type	Number of Cases	Average of Last Erythrocyte Counts in Millions
Sclerosing type.....	14	3.02
Endothelial type.....	1	2.36
Lymphoblastic type.....	6	3.06
Lymphocytic type with leukemia.....	17	2.04
Lymphocytic type without leukemia.....	3	3.76

The highest and the lowest individual leukocyte counts in each type are recorded in table 9. One patient with the sclerosing type of lymphoma had a leukocyte count of 43,800, 83 per cent of which were eosinophils.⁷ In spite of such a marked leukocytosis, which was continuous in this patient, necropsy revealed no evidence of sepsis. The most pronounced leukopenia (600 per cubic millimeter) followed intensive roentgen treatment, which was given in a vain attempt to prevent strangulation by enlarged mediastinal and cervical nodes.

It is apparent from table 10 that no constantly abnormal differential count is found except in leukemia. Occasionally, high percentages of eosinophils or neutrophils are observed in the sclerosing type, and endothelial cells are often increased in all of the types. These abnormal differential counts and the extreme variability in the number of leukocytes are valuable diagnostic aids in some cases but are not constant.

6. Miller, H. R.: The Occurrence of Leukopenia in Hodgkin's Disease, Lymphogranuloma, Am. J. M. Sc. **173**:490, 1927.

7. Weber, F. P., and Bode, O.: Abdominal Lymphogranulomatosis Maligna (Hodgkin's Disease) with High Blood Eosinophilia and Lymphogranulomatous Infiltration of the Epidural Fat, Lancet **2**:806 (Oct. 15) 1927.

It will be noted that the lowest percentage of lymphocytes in lymphatic leukemia (53 per cent) approximated the highest percentage of lymphocytes in the lymphocytic type without leukemia (48 per cent). Differentiation between these two types was made on repeated leukocyte counts and differential studies. An occasional patient with the lymphocytic type without leukemia developed the blood manifestations of leukemia before death.

The severe grades of anemia were most common in the sclerosing type and in lymphatic leukemia (table 11). Almost complete replacement of the bone marrow by lymphomatous tissue was found in two cases of the sclerosing type in which the anemia was most marked. The anemia was of the secondary type except in those persons in whom the erythrocyte count was below 1 million, at which level anemia from any

TABLE 13.—*Diseases Associated with Lymphoma*

	Sclerosing Type	Endo- thelial Type	Lympho- blastic Type	Lymphocytic Type	
				With Leukemia	Without Leukemia
Number of cases.....	46	2	19	55	14
Tuberculosis					
Cervical nodes.....	1	1
Terminal millary.....	1	2
Syphilis					
Latent.....	3	2
Aortic aneurysm.....	1	..
Erysipelas.....	2	..
Noma.....	2	..
Multiple sclerosis.....	1	..
Acute mania.....	1	..
Streptococcus peritonitis.....	1	1
Gout.....	1	..
Osteo-arthritis.....	1	..
Inguinal hernia.....	1	..
Carcinoma of the cheek.....	1	..
Hypertrophy of the prostate....	1	..

cause usually has a color index of at least 1. Table 12 gives the erythrocyte counts in the various types of lymphoma shortly before death.

The diseases associated with the lymphomas in our series are indicated in table 13. Neither arteriosclerosis nor heart failure, both of which were common in the old men with leukemia, are included. In most instances, however, the cardiovascular changes were in keeping with the advanced age.

Tuberculosis occurred in only five cases, in three of which it was miliary. Each of the other two patients had numerous cervical scars from tuberculous adenitis during childhood. Active fibrocaceous tuberculosis of the lungs was not found in any of the cases in this series.

A diagnosis of syphilis was made in six cases. In five of these, there were no clinical manifestations of the disease. The Wassermann test, however, was strongly positive in all, and in four there was a history of chancre. The sixth patient had an aortic aneurysm and a positive Wassermann reaction.

Routine examinations of the blood have led to the diagnosis of lymphatic leukemia in patients admitted to the hospital for multiple sclerosis, osteo-arthritis, strangulated inguinal hernia, and hypertrophy of the prostate, and in a fifth with gout and a carcinoma of the cheek. In none of these cases were the lymph nodes large enough to arouse suspicion when the diagnosis was first made, and two have been observed for more than a year without the development of lymphadenopathy. Such observations would seem to indicate that the blood changes often antedate noticeable enlargement of the fixed lymphatic structures in leukemia. Erysipelas, noma, streptococcic peritonitis and miliary tuberculosis were the terminal infectious lesions seen in our series. Acute mania developed in one patient.

TABLE 14.—*Manifestations of Lymphoma Observed Clinically*

	Sclerosing	Endo- thelial	Lympho- blastic	Lymphocyte Type	
				With Leukemia	Without Leukemia
Number of cases.....	46	2	19	55	14
Pleural effusion.....	18	..	6	6	4
Pruritus.....	11	..	3	5	2
Infiltration of skin.....	3	..	2	3	1
Infiltration of breast.....	5	..	3	1	..
Infiltration of nasopharynx....	1	1	3	..	1
Infiltration of stomach.....	1
Infiltration of intestine.....	1	1	1
Intestinal obstruction.....	1	1	1
Infiltration of bone.....	6	1	..	1	1
Involvement of vertebra with collapse and gibus.....	3
Involvement of nervous system..	9	1	..	3	2
Herpes zoster.....	6	1	..	1	..
Horner's syndrome.....	1	1	1
Sudden deafness.....	2	1	..
Bronchial obstruction.....	4
Chylous ascites and chylothorax	1
Obstruction of ureter.....	1	1
Hematuria.....	1
Ulcer of penis.....	2	..
Acute arthritis.....	13	..
Subcutaneous emphysema.....	1

Although the primary lesion in all types of lymphoma is no doubt in the fixed lymphatic tissue, secondary manifestations may be met with in any of the body structures. The pathologic histology is the same in the lymph nodes and in the metastatic nodules. The clinical manifestations, however, are protean and are dependent on the tissue predominantly involved (table 14).

Pleural effusion was observed in 39 per cent of patients with the sclerosing type and in 23 per cent of the whole group. This particular complication occurs so frequently that it should be anticipated and an attempt made to delay its development by roentgen treatment of the mediastinal nodes. Effusions were more frequently induced by encroachment on the great veins or by obstruction of lymphatics than by metastases or infiltration in the pleura.

Pruritus^s has long been recognized as a frequent manifestation in the sclerosing type, but it was also present in the other types in our series. We have not recognized a characteristic type of nonmetastatic skin lesion. In most cases of pruritus, long continued scratching had led to abrasions and consequent inflammatory thickening of the skin. The itching skin without local lesions was usually dry and rough.



Fig. 6.—The diffuse flat skin lesions of the sclerosing type. Enlarged inguinal lymph nodes can also be seen.

Infiltration of the skin with the formation of definite nodules was considerably less common than pruritus but occurred in all types. In the sclerosing type the nodules were flat, elevated 1 to 2 mm. above the surface, and measured from 1 mm. to 3 cm. in diameter (fig. 6). Hyperemia was confined to the lesions, and the involved skin was scaly. These lesions were definitely in the dermis and moved freely over the subcuta-

8. Miller, H. E.: Lymphogranulomatosis Cutis, Hodgkin's Disease, Arch. Dermat. **17**:156 (Feb.) 1928.

neous tissue. One of the patients with the lymphoblastic type presented innumerable bluish, globular tumors in the skin, the largest of which was less than 1 cm. in diameter. Massive leukemic infiltration of the skin, such as has been repeatedly described in the literature, occurred in one patient in our series. Extensive infiltration was present in the skin of the arms, chest, abdomen, back and legs. There was a diffuse involvement over the back and chest which gave the skin a bronze color and a leathery consistency. In many places there was distinct tumor formation. The largest of these was 10 cm. in diameter and extended 5 cm. above the surrounding skin. The surfaces of the tumors were fissured



Fig. 7.—The diffuse brawny induration of the skin over the back with two large weeping tumors. The front view shows tumors in all stages of development.

and were covered by a thick layer of dried exudate. Serum oozed from the fissured surfaces of some of the tumors, especially those beneath the breasts and in the groins (fig. 7). The involvement of the skin observed in the other cases of lymphatic leukemia and in the one of lymphocytic type without leukemia was not nearly so extensive. No instances of universal leukemia cutis were encountered in our series.

Tumors of the breast were found in nearly all types of lymphoma. Unfortunately, histologic examination of the lesions of the breast was not made. One of the tumors had the gross characteristics of carcinoma in that the nipple was retracted and fixed, there was a "pig skin" appearance about the nipple, and the only palpably enlarged lymph nodes were

in the corresponding axilla. Three of the patients were males and six were females. In the males there was involvement of the entire breast, while in the females the infiltration was localized and formed nodules. All of the lesions of the breast responded promptly to roentgen treatment.

Infiltration of the nasopharynx is often considered a characteristic feature of the lymphoblastic type (lymphosarcoma). The six cases in our series with such involvement represented four different types of lymphoma.

Infiltration of the gastro-intestinal tract⁹ by the various types of lymphoma has been reported frequently in recent years. In some instances, the lesion has apparently been limited to the stomach or bowel. The condition has been reported as "round cell sarcoma" or "lymphogranuloma." Gross gastric infiltration was found only once in our series. The case was that of a woman, aged 31, in whom there was also an involvement of the bowel, the cervical and abdominal nodes and the spleen. Lymphoblastic tumor tissue varying from 1 to 2.5 cm. in thickness involved most of the stomach wall. Roentgen examination of the gastro-intestinal tract was made of many of the patients of this series, but no other instance of gross involvement was recognized.

Unless it is extensive, involvement of the bowel in any form other than the sclerosing type is difficult to diagnose even histologically, because of the large amount of lymphoid tissue normally present. In the three cases recorded there were definite symptoms of involvement of the bowel and marked and unquestionable overgrowth of lymphoid tissue was demonstrated, once by proctoscopic examination and twice at necropsy. This group was distinct from those in which intestinal obstruction occurred.

The intestinal obstruction which occurred in three different types was chronic and progressive. In each of the cases it resulted from encroachment on the small bowel by enlarged mesenteric and retroperitoneal nodes. The nature of the condition was appreciated clinically in all cases by inference from involvement of lymph nodes elsewhere.

In the involvement of bone, lymphomas present one of their most interesting features. We have seen metastases mistaken roentgenologically for both pyogenic and tuberculous osteomyelitis. Destruction of part of the ischium without any sign of proliferative reaction was seen in one case (fig. 8A). Following roentgen treatment new bone was laid down, and a satisfactory functional result was obtained (fig. 8B). In three cases in which there was vertebral involvement (fig. 9), with the formation of angular kyphosis, the roentgenograms were prac-

9. Hayden, H. C., and Apfelback, C. W.: Gastro-Intestinal Lymphogranulomatosis, *Arch. Path* 4:743 (Nov.) 1927.

tically identical with those of tuberculosis of the spine.¹⁰ One of these patients was given roentgen treatment over the involved vertebra with little or no change in the appearance of the lesion. Laminectomy was done later in an attempt to relieve myelitis, and material removed from the diseased vertebra showed bone invaded by a tumor which had the characteristic structure and formation of the sclerosing type of lymphoma. One case of leukemia came under observation after an operation for pyogenic osteomyelitis of the left femur (fig. 10). The diagnosis had been made by the x-rays. No pus had been found at operation, and necropsy later showed many large lymphoid nodules in the bone marrow.

Organic lesions of the nervous system due to lymphoma are considered frequent by some observers,¹¹ but most discussions of the condition in textbooks fail to mention nervous lesions of any type.

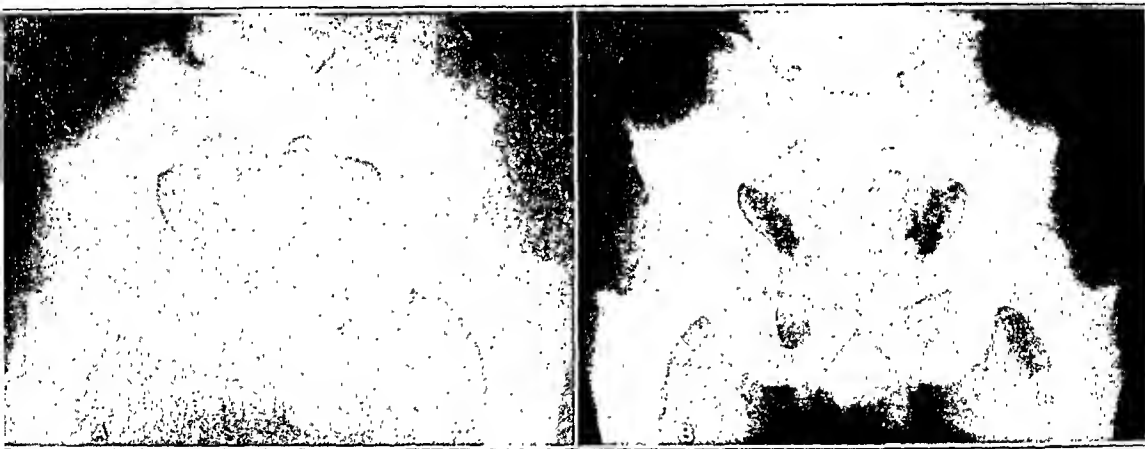


Fig. 8.—In *A*, the absence of part of the descending ramus of the ischium can best be appreciated by stereoscopic study, but a comparison with *B*, which is the same pelvis after irradiation, will give an idea of the extent of the lesion. In *B*, roentgen evidence of formation of new bone started promptly after irradiation and continued until a good functional result was obtained.

The relationship between herpes zoster¹² and lymphoma is not clear. The six instances of herpes zoster which occurred among the forty-six cases of the sclerosing type of lymphoma would not be likely to be purely coincidental. In one patient the herpes zoster developed over the distribution of the fourth right thoracic nerve and was followed in about three months by a collapse of the body of the fourth dorsal

10. Robin, N. H.: An Unusual Metastatic Manifestation of Hodgkin's granuloma, *Am. J. Roentgenol.* **14**:251, 1925.

11. Ginsburg, S.: Hodgkin's Disease, with Predominant Localization in Nervous System, Early Diagnosis and Radiotherapy, *Arch. Int. Med.* **39**:571 (April) 1927.

12. Pancoast, H. K., and Pendergrass, E. P.: The Occurrence of Herpes Zoster in Hodgkin's Disease, *Am. J. M. Sc.* **168**:326, 1924.

vertebra occasioned by a metastatic lesion. In another the herpes developed shortly before death, and the dorsal root ganglions and vertebra were examined at necropsy, but no gross evidence of metastases was discovered. In other cases postmortem examination was not possible, but there was no gross evidence of metastatic lesions in the spine or along the course of the involved nerves.

Horner's syndrome was not found frequently in our series in spite of the large percentage of cases showing involvement of the cervical nodes. In all three instances, the condition was unilateral. The syndrome comprises enophthalmos, a slight droop of the upper lid, myosis which is indifferent to cocaine and unilateral hyperhidrosis, all of which

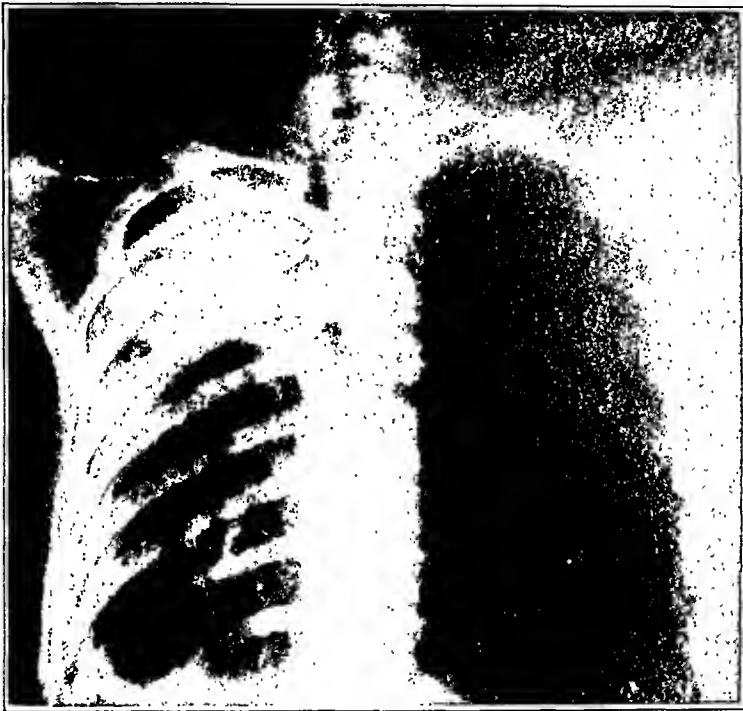


Fig. 9.—Collapse of the fourth dorsal vertebra and opacity of the right lung.

may be the result of paralysis of the cervical sympathetics. The elasticity of the enlarged nodes and the fact that the tumor shows little tendency to invade perilymphatic tissue are the chief reasons for the rarity of pressure paralysis in lymphoma.

Sudden deafness has occurred in some of our patients with disease of the hematopoietic system. In most instances, it has appeared in association with bleeding from the mucous membranes or hemorrhages into the skin. Although the pathologic basis was never established, it was assumed that such deafness was in some way induced by hemorrhage.

Lesions of the nervous system not falling in any of the foregoing groups have apparently been produced by encroachment rather than actual invasion or metastases. Myelitis and paralysis of part of the

brachial plexus, of the sixth nerve, of the eleventh nerve, of the vagus and of a part of the lumbosacral plexus were noted in our series. Hemiplegia developed in a child of 5 years with leukemia. The exact cause was not determined.

In two patients the major complaint was pain, in one extending down the legs and in the other encircling the lower part of the abdomen. Neither of these patients showed loss of sensation nor change in the reflexes. They were not included in the group showing organic nervous lesions, although root pain was considered the most plausible explanation for the symptoms. Another patient with a metastasis in the ischium had pain much like that in sciatica.

Partial bronchial obstruction was seen in four cases of the sclerosing type. In each, the respiratory difficulty was due to a mediastinal tumor. The symptomatology strikingly resembled that of bronchial asthma.

Chylous ascites and chylothorax occurred in one instance in which a solid mass of enlarged nodes extended from the left cervical region into the left axilla. Hydronephrosis from partial obstruction of the left ureter was discovered in two cases at necropsy. A gross and persistent hematuria appeared in one patient. Cystoscopic examination showed bloody urine coming from both ureters. The pyelograms were normal. Two old men with leukemia developed ulcers of the penis while under observation. In each, the ulcer was indurated and painless. Both were repeatedly examined for *spirochaeta pallida*, but the results were negative. In one, a biopsy revealed only closely packed lymphoid cells.

Acute arthritis occurred in thirteen of the twenty patients with lymphatic leukemia under 21 years of age.

Subcutaneous emphysema extending from the zygoma to the shoulder was observed in a boy, aged 6 years, with the sclerosing type of lymphoma. The cervical nodes were enlarged, but there was no roentgen evidence of metastatic lesions in the lungs.

Table 15 was compiled for the purpose of conveying some idea of the widespread pathologic changes in the various types of lymphoma. In all of the cases there was an involvement of some of the lymph nodes, and in a vast majority there was a significant increase in weight of the spleen, and histologic changes were demonstrated. Involvement of other organs and tissues varied somewhat as to frequency and as to the nature of the lesions in the different types. In the sclerosing and endothelial types the lesions, apart from those of the fixed lymphatic tissue, were in the nature of discrete nodules. Organs in which there was an infiltration of only a few lymphocytes were not considered to be involved. The term metastasis seemed appropriate for such discrete nodules. The recognized metastases were nearly all gross; some were rounded with well defined borders, while others were invasive with irregular margins, but all showed the same histologic structure as the

lymph nodes. Some of the lesions of the lymphoblastic type were discrete nodules with localized destruction of the parenchyma of the involved organ, while others were more in the nature of an infiltration, with lymphoid cells surrounding the vessels or arranged in rows between the parenchymatous elements of the involved organ. In the lymphocytic type, both with and without leukemia, either perivascular or intercellular infiltration of lymphoid cells was common, while the formation of distinct nodules was correspondingly uncommon.

Leukemic infiltration of some degree was found in all cases of lymphatic leukemia, and its extent more nearly paralleled the duration

TABLE 15.—*Tissues Showing Involvement Microscopically*

	Sclerosing Type		Endothelial Type		Lymphoblastic Type		Lymphocytic Type			
							With Leukemia		Without Leukemia	
	A*	B†	A	B	A	B	A	B	A	B
Lymph nodes.....	15	15	1	1	5	5	19	19	2	2
Spleen.....	15	12	1	0	5	3	19	19	2	1
Bone marrow.....	4	1	1	1	1	1	10	10	1	0
Liver.....	14	4	1	1	5	3	17	17	2	2
Kidney.....	15	3	1	0	1	1	17	15	2	1
Suprarenal.....	11	1	1	0	2	2	14	6	2	2
Heart.....	13	0	1	0	4	1	13	5	2	1
Pericardium.....	3	3	2	1	9	4	1	1
Adventitia of aorta....	6	9	1	0	1	0	9	2
Lungs.....	14	7	1	1	4	2	14	10	1	0
Stomach.....	2	1	2	1
Intestine.....	2	1	2	1	7	4
Pancreas.....	12	2	1	0	4	3	13	2	2	2
Gallbladder.....	1	1	2	1
Peritoneal fat.....	1	1	3	3
Prostate.....	2	0	1	0	1	0	6	4	1	0
Bladder.....	2	0	1	3	6	6
Ureter.....	1	1
Uterus.....	1	0	1	1
Thyroid.....	1	1
Thymus.....	1	..	2	2
Skin.....	1	0	1	1	1	1	1	1
Bone.....	2	2	1	1	1	1
Conjunctiva.....	1	1
Peritoneum.....	2	2

* A indicates number of cases in which histologic sections of the indicated organs were available for our study (cases seen at necropsy only).

† B indicates number of instances in which infiltration or metastases were found.

than any other single feature. Lymphatic leukemia in childhood was rapidly fatal, frequently with hemorrhages of the skin and mucous membrane and high fever, whereas in adults it was essentially a chronic disease lasting about three years and not accompanied by hemorrhages except terminally. Yet the pathologic changes in these two conditions varied only slightly. The cells making up the enlarged lymphoid structures in children were larger, on an average, and often appeared more immature than those of lymph nodes in adult lymphatic leukemia. The difference in the fixed lymphatic cells of leukemia in the child and the adult was no greater than that seen when the lymphocytes of the normal blood smear of a child are compared with those of an adult. Regardless of age the viscera were usually less extensively infiltrated in the cases of short duration than in those of years' standing.

It is at once apparent from the table that a great variety of organs and tissues was involved in our series. In complete necropsies the abdominal and thoracic viscera were sectioned, and in addition sections were taken from other tissue which showed evidence of gross pathologic change. Some of the older necropsies were not complete, and a few of the sections that were unsatisfactory were discarded. Definite metastases are readily recognized in the gross so that the figures for the sclerosing and endothelial types are probably quite accurate, even though some of the organs were not sectioned for histologic study. The gross evidence is not so reliable in leukemia. It seems quite likely



Fig. 10.—There is a punched-out appearance in the neck and upper shaft of the left femur. The site of an operation for osteomyelitis can be seen at a lower level.

that leukemic infiltration is almost universal in long-standing cases, and if more organs were sectioned more infiltration would be found. We have found lymphoid infiltration microscopically in chance sections from the bladder, peritoneum, peritoneal fat and uterus. In one instance, a leukemic infiltration of the conjunctiva was demonstrated (fig. 11). Leukemic involvement of this structure has been reported in the literature.¹³ The pancreas and heart seemed to be relatively immune,

13. Meller, J.: Die lymphomatösen Geschwulstbildungen in der Orbita und im Auge, *Arch. f. Ophth.* **62**:130, 1905.

and the most marked infiltrative lesions were observed around the portal veins and between the kidney tubules.

It is worthy of special mention that 50 per cent of the lungs examined from patients with the sclerosing type of lymphoma showed definite metastases.

DISEASES SIMULATED BY LYMPHOMA

*Dermatitis.*⁸—The danger of overlooking lymphoma in a patient complaining of itching has been stressed repeatedly. The firm, elastic, freely movable, non-tender nodes of lymphoma are in distinct contrast to the soft, tender nodes resulting from the drainage of acute skin lesions or the fibrous, shrunken, and anchored nodes of ancient infection. Irrespective of whether or not the skin lesions were the result of scratching or metastases to the skin, the nodes were sufficiently characteristic in all of our cases to establish the diagnosis without difficulty.

*Mycosis Fungoides.*¹⁴—In lymphatic leukemia large, warty skin lesions may occur which grossly are not distinguishable from the lesions of mycosis fungoides (fig. 12). Indeed, there is considerable discussion among dermatologists as to



Fig. 11.—Boggy masses of lymphoid infiltration in the conjunctiva in lymphatic leukemia.

whether or not these conditions are identical. We have had two cases in which the lesions were grossly similar. In one case the histologic composition of the enlarged lymph nodes and of the skin tumors was that of the lymphocytic type of lymphoma, and the blood manifestations were those of lymphatic leukemia, while in the other the lymph nodes were not enlarged, the blood was normal, and the histologic manifestations of the skin tumors were those of granulation tissue and inflammatory cells (fig. 13).

Tumors of the Breast.—Most of the lesions of the breast occurring in patients with lymphoma resemble mastitis more than carcinoma. If one appreciates the fact that involvement of the breast occurs in lymphoma, there will usually be little difficulty in diagnosis. However, the diagnosis may be largely a matter of inference from enlarged lymph nodes elsewhere because of the notorious difficulty in determining the characteristics of a small tumor in a large breast. In one of our patients, a woman, aged 63, the condition was promptly diagnosed carcinoma of the breast by an able surgeon. The right breast was edematous, with the

14. Highman, W. J.: Mycosis Fungoides and Kindred Conditions; the Criteria of Their Diagnosis, Arch. Dermat. & Syph. **13**:522 (April) 1926.

"pig skin" appearance about the areola, a retracted nipple, and a 3 cm. mass of hard lymph nodes in the right axilla. The abdomen was distended with fluid, and a mass could be felt in the left upper quadrant. The only palpable lymph nodes were in the right axilla, but there was a history of a node having been removed from the left cervical region six months before. The microscopic diagnosis, which we were able to confirm, was the lymphoblastic type of lymphoma. Irradiation caused a prompt decrease in the size of the axillary nodes; the edema disappeared from the breast, the skin became normal and the nipple freely movable.



Fig. 12.—Mycosis fungoides. The resemblance to leukemic infiltration as shown in figure 7 should be noted.

Without the previous biopsy, we would certainly have concurred in the diagnosis of carcinoma of the breast.

Tumor of the Spinal Cord.—Symptoms of myelitis occurred in one of our cases but were associated with a definite metastatic lesion of the vertebral body at the corresponding level, and a tumor of the spinal cord was therefore not considered. The diagnosis of a tumor of the cord was, however, considered in two other cases in which there was excruciating pain. In one the pain extended down the legs, and in the other it encircled the lower part of the abdomen. The signs of myelitis did not develop in either patient.

Paroxysmal Tachycardia.—In one case, which was reported in detail by Dr. V. C. Graber,¹⁵ a nodal paroxysmal tachycardia developed, and necropsy showed that the vagi were compressed by enlarged mediastinal lymph nodes. There was marked myelin degeneration of both vagi and especially of those branches entering into the cardiac plexus.

*Carcinoma of the Stomach.*¹⁶—Two elderly men with lymphatic leukemia were sent to the hospital with the diagnosis of carcinoma of the stomach. Such errors



Fig. 13.—Granulomatous tissue making up the nodules in mycosis fungoides.

may be easily avoided by examining the blood or by a roentgen study of the stomach. The similarity between lymphatic leukemia and carcinoma of the

15. Graber, V. C.: Paroxysms of Tachycardia Occurring in Case of Hodgkin's Disease in Which Vagus Nerves Were Degenerated by Pressure of Enlarged Mediastinal Glands, *Am. Heart J.* **1**:564, 1926.

16. Holmes, G. W.; Dresser, R., and Camp, J. D.: Lymphoblastoma (Malignant Lymphoma); Its Gastric Manifestations with Special Reference to Roentgen Findings, *Radiology* **7**:44, 1926.

stomach is really superficial. When there is an actual invasion of the stomach wall, however, by one of the noncirculating types, the correct clinical diagnosis may be established only by the discovery of an involvement of the peripheral lymph nodes. Such circumstances obtained in one of our cases of the lymphoblastic type. The stomach was diffusely involved, and the cervical nodes were enlarged on both sides. These nodes were, however, too extensively involved to be confused with the ordinary "Virchow gland." Without involvement of the peripheral lymph nodes, the differentiation is apt to be impossible clinically.

Carcinoma of the Bowel.—One of our patients passed enormous amounts of slightly changed blood in the stool. There was a large irregular mass filling most of the left half of the abdomen, and the patient gave a history of obstinate constipation. The diagnosis happened to be easy, because the blood manifestations were those of leukemia and all of the peripheral lymph nodes were enlarged. In another patient, there were multiple lymphoid tumors of the bowel wall with ulceration of the mucosa over them.

Colitis.—One patient was sent to the hospital with a diagnosis of colitis. There was almost continuous diarrhea for eight months and a loss of 60 pounds (27.2 Kg.) in weight. The stools contained considerable fat but little mucus. There had been several frank hemorrhages. Examination revealed infiltrative lesions of the skin and enlarged lymph nodes in the inguinal regions and in the neck. The histologic structure of an excised inguinal node was that of the sclerosing type of lymphoma. Irradiation had no appreciable effect on the diarrhea. At necropsy, there was a uniform enlargement of the lymph nodes in the mesentery. There were no collections of fat in the lymphatics of the bowel wall, but the patient's diet had been largely carbohydrate for weeks before death, and he had eaten little during the last several days of life. The bowel wall showed no gross evidence of metastasis. A few small mucous cysts were noted in the submucosa. It is believed that the enlarged mesenteric nodes obstructed the flow of fat in the lymph channels and thereby induced the marked emaciation and possibly the diarrhea.

In another patient with the symptoms of colitis, an extensive increase of the lymphoid tissue of the bowel was seen by the proctoscope. The enlarged lymph follicles had the appearance of papillomas.

Osteomyelitis.—One of our patients had been operated on elsewhere for pyogenic osteomyelitis. A blood count would have prevented the error. Roentgen examination showed a disturbance in the medullary portion of the left femur.

*Tuberculosis of the Spine.*¹³—The diagnosis of tuberculosis of the vertebral bodies was made by the roentgenologist in three of our patients with the sclerosing type of lymphoma. In the one who came to necropsy, a metastatic lesion was found responsible for the destruction of the vertebra. In another, the diagnosis was established by a biopsy. The lesion in the third was assumed to be that of lymphoma on the basis of the observations elsewhere and in the absence of clinical manifestations of tuberculosis.

Tuberculosis of the Lungs.—Four patients in our series were sent to us from sanatoriums for the treatment of tuberculosis. In all, the condition was originally diagnosed tuberculosis. The lungs were frequently invaded by metastatic lesions (50 per cent of our fourteen necropsies) in the sclerosing type of lymphoma. The clinical resemblance to tuberculosis may be striking. In one of the patients with collapse of a vertebral body, there was an extensive involvement of the right lung. There was no expansion of the right side of the chest; the percussion note was flat, and the breath sounds were faint and tubular (fig. 14 A). A needle was inserted and a solid lung encountered but no fluid obtained. However, there were

no râles, no evidence of cavitation, no sputum, and no history to suggest pulmonary tuberculosis. So extensive a tuberculous pneumonia could hardly have occurred without the patient's knowledge. On the basis of the foregoing observations, we felt that tuberculosis could be excluded in spite of a solid lung and a roentgen diagnosis of tuberculosis of the spine, and later developments have proved this assumption to be correct at least so far as the vertebral involvement is concerned.

Tuberculosis of the Peritoneum.—In one patient a diagnosis of tuberculous peritonitis was made on the bases of a loss of 25 pounds (11.3 Kg.) in weight, abdominal discomfort, an irregular fever, sweats and ascites. An enlarged lymph node was removed at operation which showed the histologic picture of the sclerosing type of lymphoma. There was no enlargement of the peripheral nodes.

Serofibrinous Pleurisy.—Pleural effusions are common in all types of lymphoma, but usually there is sufficient adenopathy to prevent errors in diagnosis. One of our patients gave a history of having had a thoracentesis and stated that tubercle bacilli were found in the aspirated fluid. A diagnosis of lymphoma seemed quite

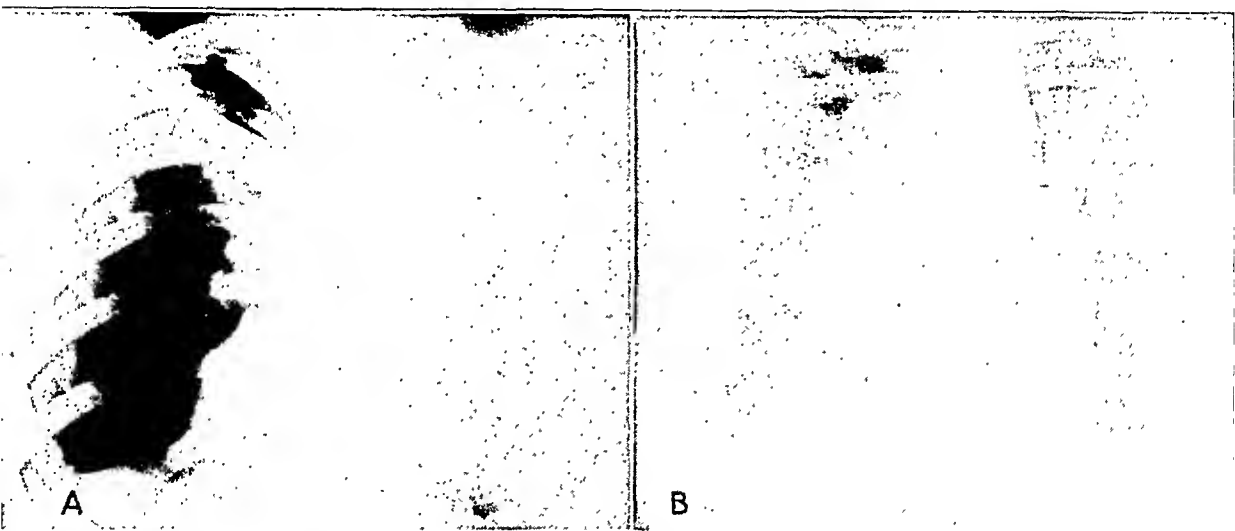


Fig. 14.—*A*, the sclerosing type of lymphoma involving the right lung. *B*, involvement of the mediastinal lymph nodes with encroachment on the trachea or bronchi to produce asthma-like symptoms.

obvious because of many enlarged nodes in the neck. A biopsy was done, however, to remove all doubt, and the sclerosing type of lymphoma was discovered. No evidence of tuberculosis of either the lung or the pleura was found at necropsy five months later.

Bronchial Asthma.—The diagnosis of bronchial asthma was made in four of the patients in our series. In all, there was an involvement of the peribronchial lymph nodes early in the course of the disease. Each had the sclerosing type of lymphoma and later had a generalized adenopathy. One of these patients is worthy of brief mention because of the striking resemblance of the clinical picture to that of bronchial asthma. She gave a history of having had hay-fever for years. A short time prior to admission to the hospital, attacks of nocturnal dyspnea began to appear which were accompanied by cough and the expectoration of frothy sputum. During the attacks, sibilant and sonorous râles were heard throughout both lungs. Because the attacks were not relieved by epinephrine, a roentgen examination of the chest was made (fig. 14*B*), and an enlargement of the hilum nodes was discovered.

Rheumatic Fever.—It is of interest to note that 65 per cent of the patients with lymphatic leukemia under 21 years of age had acute symptoms of involvement of the joints. This feature was not observed in the older patients with lymphatic leukemia, nor was it noted in the other forms of lymphoma. Neither the cause nor the nature of the joint manifestations is understood. In one case the synovial membrane was examined histologically at necropsy about three months after the onset of acute symptoms, and no pathologic change was found. Histologic examination was not made in the other cases, and none of the joints was aspirated. It was assumed that hemorrhage was the most likely cause for the swelling, redness, effusion and pain in such joints. The involvement in nearly all cases was multiple and shifted from joint to joint much like rheumatic fever. In one case there was a marked anemia and a loud hemic heart murmur, but no valvular disease was found at necropsy. In a number of instances, the diagnosis of rheumatic fever was made prior to the admission to the hospital.

Still's Disease.—Still's disease is simulated by those cases of lymphatic leukemia in childhood in which the joint symptoms last for a considerable period and in which the enlargement of the spleen and the lymph nodes is only moderate. We have seen such an error made on one occasion.

Primary Syphilis.—A leukemic infiltration of the glans penis leading to the formation of an indolent ulcer is a rather unique observation which is difficult to explain, especially in the absence of other infiltration of the skin or mucous membrane. Priapism was not present in either case.

Hemolytic Icterus.—One of our patients, a young man, aged 24, complained of attacks of abdominal distress, which had appeared at intervals for four years. The attacks came on gradually with a feeling of indisposition and anorexia followed by nausea and, at times, vomiting. Pain and tenderness were noted under the right costal margin and a feeling of fulness in the corresponding location on the left side. A slight jaundice would appear in forty-eight hours and gradually disappear after a week. After two or three weeks the appetite would return, and the patient would consider himself well. At first these attacks came once a year but later occurred every few months. When first examined, the spleen was somewhat tender and extended to the level of the umbilicus. The tenderness was particularly noted during the attacks. The liver was enlarged and also tender during the attacks. There were five large lymph nodes in the left axilla, the largest measuring 4 cm. in diameter. These nodes were observed to increase in size during periods of abdominal distress. Repeated tests failed to show increased fragility of the erythrocytes. The histologic examination of an excised node established the diagnosis of the sclerosing type of lymphoma. The patient died outside the hospital and, unfortunately, a necropsy was not obtained.

Aplastic Anemia.—A woman, aged 58 years, with an enlarged spleen and a severe aplastic anemia of unknown etiology was kept alive for two months by transfusions. Six days before her death she developed greatly enlarged nodes in the cervical, axillary and inguinal regions. A diagnosis of lymphoma (sclerosing type) was apparent when the enlarged nodes appeared, and this was confirmed at necropsy. The erythrocyte counts ranged from 1,800,000 to 1,010,000; hemoglobin, from 29 to 19 per cent; leukocytes, from 3,700 to 2,200; and the hematocrit, from 13 to 10 per cent. Polymorphonuclear neutrophils were as high as 64 per cent after transfusion and as low as 42 per cent at other times. There was a greatly reduced platelet count, and the thrombocytocrit value varied between 0.10 and 0.15 per cent (normal, from 0.4 to 0.6 per cent). The reticulocytes varied between 1.3 and 0.1 per cent, and there were no nucleated erythrocytes.

At necropsy, the bone marrow was almost completely replaced by tissue showing the histologic characteristics of the sclerosing type of lymphoma.

Hypernephroma.—A persistent hematuria and enlarged cervical lymph nodes in one case led us to suspect a hypernephroma with metastases. A node was removed which showed the histologic picture of lymphoma of the lymphocytic type. The pyelograms of both kidneys were normal. The lymphocytic type of lymphoma in our series has rarely been associated with discrete nodules in the parenchymatous organs. Whether or not the infiltration of lymphoid cells between the kidney tubules could induce an extensive hematuria is a matter for speculation. The bleeding was not affected by irradiation, and the patient has not come to necropsy.

Malta Fever.—When a patient has a fever of from 102 to 105 F. for thirty days, with an enlarged spleen as the only abnormal physical manifestation, and a marked leukopenia, there are many possibilities to be considered in diagnosis. If, as occurred in one of our cases, such a bout of fever repeats itself four times, the possibilities are reduced to lymphoma, undulant fever, and perhaps kala-azar. Blood cultures and agglutination tests excluded typhoid and undulant fever. Kala-azar has never been reported in a permanent resident of the central United States. In retrospect, the diagnosis of lymphoma should have been easy. Biopsy, however, was not possible, and we were aware of having made a diagnosis of the splenic type of lymphoma in two similar patients in the past, both of whom recovered. The former cases were probably unrecognized instances of undulant fever.

COMMENT

In the foregoing series of 150 consecutive cases of lymphoma, the clinical manifestations were protean and were dependent on the involvement of many anatomic structures. The great range of the clinical varieties was a striking feature. It would therefore seem that the prevailing conception regarding the usual manifestations of lymphoma has been taken from the rather brief discussions of the disease appearing in textbooks.

Many of the most marked variations in course and clinical manifestations occurred in patients with the same basic pathologic change. From this study, it would appear that the popular division of lymphatic leukemia into acute and chronic forms gives an exaggerated idea of the basic differences between the two. As in diabetes mellitus, we may be dealing with a disease that is borne much better by the adult than by the child.

A marked clinical variation without corresponding qualitative changes in the basic pathologic histology was also seen in the "acute" and "chronic" cases of the sclerosing type of lymphoma. Here, again, the acuity of the disease tended to have an inverse relation to the age.

The clinical manifestations of the sclerosing, endothelial, lymphoblastic and the lymphocytic type without leukemia may be practically identical.

The conditions discussed in this communication may or may not eventually prove to be a variation of the same disease entity. They

differ in respect to the condition of the circulating blood, the type of cell predominating in the enlarged lymphoid structures, and to a certain extent, in the type of lesion produced in the viscera. In other respects, there is a striking similarity. All primarily involve the fixed lymphatic structures and terminate fatally. Fever of an almost specific variety may occur in any type. In all there may be a secondary involvement of skin, bones, nervous tissue, breast and viscera. The basic metabolic rate is often increased in all types. The histologic variation in the various types of lymphoma is no greater than that seen in carcinoma of the stomach.

THE USE OF EPINEPHRINE AS A DIAGNOSTIC TEST FOR ANGINA PECTORIS

WITH OBSERVATIONS ON THE ELECTROCARDIOGRAPHIC CHANGES
FOLLOWING INJECTIONS OF EPINEPHRINE INTO NORMAL
SUBJECTS AND INTO PATIENTS WITH ANGINA
PECTORIS *

SAMUEL A. LEVINE, M.D.

A. CARLTON ERNSTENE, M.D.

AND

BERNARD M. JACOBSON, M.D.

BOSTON

Some years ago one of us (S. A. L.) was called to see a patient with angina pectoris who was at that time experiencing a severe attack of bronchial asthma. Epinephrine, 0.5 cc., was administered subcutaneously, and after several minutes the patient developed an attack of severe anginal pain. Some time later, O'Hare,¹ in studying the effect of various drugs on arterial hypertension, observed that epinephrine produced a seizure of typical anginal pain in a patient with angina pectoris. It therefore seemed desirable to us to investigate the effect of epinephrine on patients with angina pectoris, for if all such patients should react to the drug by developing typical pain, it would follow that this knowledge might be applied for diagnostic purposes. It is not inferred that if this test is valid it need be tried in cases in which the diagnosis is certain, for then one would only be inducing an unnecessary attack of pain in a condition in which it is well known that any attack may have serious consequences. Numerous instances arise, however, in which the diagnosis of angina pectoris is by no means certain. This is particularly true when the symptomatology suggests the possibility of disease of the gallbladder, stomach or duodenum. Occasionally it is difficult to tell at the bedside whether pain or discomfort in the lower sternal region is due to upper abdominal or coronary artery disease. Here, certainly, it is important to decide whether the patient needs medical or surgical care.

Furthermore, there are instances in which it is certain that gallstones are present, and yet it is suspected that angina pectoris may also be

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* From the Medical Service of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. O'Hare, J. P.: Personal communication to the authors.

present. More definite proof that both conditions exist would naturally aid in deciding whether it was warranted to subject the patient to a major surgical operation.

METHOD

To determine the degree of regularity with which epinephrine produces typical attacks of pain in patients with angina pectoris, doses of 1 cc. of the drug were given subcutaneously to eleven such patients. For purposes of control similar doses of epinephrine were administered to ten young adults and to ten patients of the same age group as those with angina pectoris but without symptoms referable to the cardiovascular system. In each instance the subject was placed at rest in the recumbent position for thirty minutes or longer before the observations were begun. The same position was maintained throughout the experiment. After the systolic blood pressure had reached a constant level as determined by four or five consecutive readings, a control electrocardiogram was taken. Then, after again recording the blood pressure, the epinephrine was injected. Determinations of the blood pressure were made at intervals of two or three minutes for the first hour of the experiment and at five minute intervals for the remainder. A detailed record was kept of all subjective and objective responses on the part of each patient, and electrocardiograms were taken at frequent intervals. In each instance the observations were continued until the blood pressure had returned to its resting systolic level. If, at this time, the electrocardiogram still showed changes from the control tracing, additional records were taken at intervals of several hours.

RESULTS

A summary of the results obtained is presented in tables 1, 2 and 3. In ten of the eleven patients with angina pectoris a typical attack of pain resulted from the administration of epinephrine. The average time required for the development of pain was twenty minutes, with extremes of three and thirty-three minutes. The pain in each instance appeared a few minutes before the maximum systolic blood pressure was attained and lasted from five to thirty-seven minutes, with the exception of one case in which it remained for one hundred and ten minutes. In seven patients there was characteristic radiation of the pain, while in two, who had had radiating pain in some spontaneous attacks, there was only localized pain during the experiment. In four cases the attack was brought to an end by nitroglycerin or amyl nitrite, while in one, because the nitrites gave only transient relief, one-quarter grain (0.016 Gm.) of morphine was administered hypodermically. The single patient who did not respond to the test became extremely upset when the purpose of the experiment was explained to him, and basal blood pressure readings were obtained only after more than an hour's rest. Then a few minutes after the injection of the drug he became excited, restless and very angry. As a result, the systolic blood pressure rose to over 200 mm.; but on reassuring the patient and removing the electrocardiograph electrodes, it quickly dropped to its resting level. No pain was experienced. It is felt that this experiment can

TABLE 1.—Results in Patients with Angina Pectoris

Name	Age	Diagnosis*	Duration of Angina Pectoris	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure	Maxi- mum Pulse	Maxi- mum Pulse Rate	Onset of Pain, Minutes After Injection	Location of Pain	Radiation of Pain	Duration of Pain, Minutes	Nitrites	Maximum Change in Amplitude of T-2, Mm.†
M. S.	52	Pulmonary emphysema; diabetes mellitus	3 yr.	Delayed A-V con- duction	125	220	60	26	22	Retrosternal	To left arm	8	+	+1.3
S. G.	53	Chronic con- stipation	8 mo.	Sinus rhythm; left axis deviation; T-1, 2, 3 diphasic	135	210	63	41	23	First left interspace	To above left scapula	17	+	+5.0
I. S.	46	Parkinson's disease	4 yr.	Sinus rhythm; left axis deviation	125	210	65	50	3	Retrosternal	0	5	0	+3.8
H. N.	73	Carcinoma of ascending colon; secon- dary anemia	4 wk.	Sinus rhythm; left axis deviation; T-3 iso-electric	115	140	29	5	25	Retroxiphoid	0	20	0	+1.2
H. H.	65	Duodenal ulcer	7 mo.	Sinus rhythm; T-3 inverted	133	194	40	36	22	Retrosternal; upper part of back	To left axilla	26	+	+1.4
G. G.	56	Pulmonary emphysema	3 mo.	Sinus bradycardia; R-3 notched; T-3 inverted	116	162	37	35	28	Second right interspace	To inter- scapular region	20	0	+1.3
J. E.	50	Psoriasis	3 wk.	Sinus rhythm; "cov- ing" lead I; T-1 inverted; T-2 and T-3 diphasic	130	142	6	21	7	Retrosternal	To jaws	16	+	+0.8
E. A.	50	Arteriosclerosis	4 yr.	Sinus rhythm; left axis deviation; T-1 diphasic; T-2 diphasic	148	185	40	27	33	Retrosternal	0	12	0	+1.4
M. B.	53	Adenoma of prostate	5 wk.	Sinus rhythm; left axis deviation; P-3 and T-3 inverted	122	190	54	46	8	Retrosternal	To left arm	37	0	+3.4
J. G.	55	Umbilical hernia	8 mo.	Sinus bradycardia; left axis deviation; T-3 inverted	90	190	60	38	25	Retrosternal	To jaws	110	+	+0.5
Average.....					126.4	184.3	45.4	32.5	20.1			27.1		+2.01

* In addition to angina pectoris.

† After the injection of epinephrine.

TABLE 2.—Results in Elderly Patients Without Angina Pectoris

Name	Age	Diagnosis	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure*	Maximum Pulse Pressure Increase*	Maximum Pulse Rate Increase*	Maximum Change in Amplitude of T-2, Mm.*
I. L.	63	Carcinoma of cecum; secondary anemia	Sinus rhythm; few premature beats	130	176	44	46	+0.5
M. S.	42	Lobar pneumonia; syphilis of central nervous system	Sinus rhythm	130	175	47	15	+0.2
L. T.	61	Epldermophytosis	Sinus rhythm; left axis deviation; T-3 diphasic; intraventricular block	150	211	90	20	+3.0
H. G.	50	Multiple sclerosis	Sinus rhythm	120	151	36	18	-2.3
D. P.	51	Chronic lymphatic leukemia	Sinus rhythm; T-3 inverted; slurring R-2	100	131	31	21	-0.3
E. R.	43	Psycho-neurosis	Sinus rhythm	122	130	16	11	-1.4
M. R.	62	Lobar pneumonia; convalescent	Sinus rhythm; left axis deviation	125	181	49	30	+1.4
R. R.	58	Dibothrycephalus latus infestation	Sinus rhythm	133	138	5	27	-1.0
S. R.	63	Carcinoma of stomach; secondary anemia	Sinus rhythm	120	156	38	21	-0.8
M. F.	55	Secondary anemia	Sinus rhythm; T-3 inverted	120	141	22	20	-0.7
Average.....				125.0	163.5	38.1	22.9	-0.01

* After the injection of epinephrine.

TABLE 3.—Results in Young Adults

Name	Age	Control Electrocardiogram	Resting Systolic Pressure	Maximum Systolic Pressure*	Maximum Pulse Pressure Increase*	Maximum Pulse Rate Increase*	Maximum Change in Amplitude T-2, Mm.*
B. J.	23	Sinus rhythm	114	146	38	12	-1.2
E. K.	21	Sinus rhythm	120	169	47	18	-1.8
F. K.	24	Sinus rhythm	116	144	27	25	+0.6
A. M.	30	Sinus rhythm	101	132	18	52	+1.5
O. E.	27	Sinus rhythm; diphasic T-3	122	133	24	16	+0.2
S. H.	22	Sinus rhythm	108	174	54	37	+1.1
D. S.	33	Sinus rhythm	98	130	36	34	+0.4
J. R.	23	Sinus rhythm	116	146	20	14	-3.0
A. E.	27	Sinus rhythm; ventricular premature beats; T-3 diphasic	120	170	53	27	-2.5
A. R.	26	Sinus rhythm	120	136	16	22	-3.3
Average.....			113.8	148.5	33.3	24.7	-0.8

* After the injection of epinephrine.

hardly be used in evaluating the results of the investigation. Four of the patients who developed anginal pain with 1 cc. of epinephrine had been given 0.5 cc. on a previous occasion without such effect.

None of the elderly control subjects or young adults experienced anginal pain. One of the former group, however, did report a sensation of dull oppression behind the xiphoid three minutes after the injection. This lasted for six minutes and disappeared before the systolic pressure had reached its peak. In addition, one patient from each of the two control groups reported momentary sticking, precordial pain at the height of epinephrine effect.

Blood Pressure.—In the ten patients with angina pectoris who reacted to the test with an attack of typical pain, there was an average rise in systolic blood pressure of 58 mm. of mercury, with limits of 12 and 100 mm. In six patients the rise amounted to more than 65 mm. The systolic pressure in the group of elderly controls showed an average rise of 39 mm. of mercury, with limits of 5 and 94 mm. In seven patients the rise was over 33 mm. There was an average rise of systolic pressure in the group of young adults of 33 mm., with extremes of 16 and 66 mm. Six patients had an increase of 30 mm. or more. The average time required for the attainment of the maximum systolic pressure was between twenty and twenty-four minutes in all three groups of cases. In the ten patients with angina pectoris there was an average increase in pulse pressure of 45 mm. of mercury. In the elderly controls there was an average increase of 38 mm., and in the young adults the average was 33 mm. of mercury. In general, therefore, it may be said that the rise in systolic blood pressure and pulse pressure was somewhat greater in the patients with angina pectoris than in the other two groups.

Pulse Rate.—The average pulse rate increase in the ten patients with angina pectoris was 33 beats per minute. For the elderly controls the average increase was 23 beats per minute, and for the young adults it was 25 beats per minute. Here again the effect, in general, was greater in the patients with angina pectoris than in the others.

Symptoms and Signs.—Practically every patient showed symptoms and signs characteristic of the effect of epinephrine. These included tremor, palpitation, sweating, pallor, flushing, nervousness, weakness and pulsations in the neck and epigastrium. Usually these symptoms and signs were of only moderate severity, and none of the patients with angina pectoris displayed the marked reactions which occur in persons sensitive to epinephrine.

Electrocardiographic Changes.—The literature contains few reports of electrocardiographic observations during attacks of angina pectoris.

Bousfield² obtained a record on a patient with aortic insufficiency during a spontaneous attack which showed block of the right branch of the bundle of His. The curve taken after the pain had subsided showed only upwardly convex S-T intervals and sharply inverted T waves in leads II and III with no conduction defect. Feil and Siegel³ obtained records during the attack in four patients, the pain being produced by mild exercise in three instances and occurring spontaneously in one. Three of these showed inversion of the S-T interval in leads I and II during the pain. One showed increased amplitude of the T wave in lead II. With the cessation of pain, the record in each instance returned to normal. One patient showed no electrocardiographic changes during the attack.

A detailed study was made of all electrocardiograms of each patient in the present investigation. In none of the groups were there appreciable or constant changes in the P wave amplitude, P-R interval, QRS complex, Q-T duration or in the contour of the S-T interval. In a few patients a preexistent sinus arrhythmia was accentuated, and in others sinus arrhythmia was initiated by the drug. Ectopic beats of nodal, auricular and ventricular origin were produced with equal incidence in all three groups of cases, beats of ventricular origin being the most commonly observed in each group. One patient with angina pectoris who had a normal control electrocardiogram showed nodal rhythm in two records taken at the height of the epinephrine effect. One patient with a P-R interval of three-tenths seconds in the control tracing developed ventricular tachycardia at the onset of anginal pain (fig. 1). Nitroglycerin was given immediately, and a curve taken two minutes later showed a return to the delayed A-V conduction of the control record. In the other patients no abnormalities of rhythm, except ectopic beats, were observed.

Particular attention was paid to the amplitude of the T wave in all records because this wave is clinically important from the point of view of disease of the coronary artery. Each patient with angina pectoris showed an increase in the amplitude of the T wave in lead II after the injection of epinephrine. The average increase observed was 2 mm., with extremes of 0.5 and 5 mm. Figure 2 shows the type of response of this group. The T wave in lead II showed a diminution of amplitude in six of the elderly controls and an increase in the other four, the average for the entire group being a diminution of 0.04 mm. with extremes of minus 1.9 and plus 3.9 mm. In the young adults (fig. 3),

2. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, *Lancet* **2**:457 (Oct. 5) 1918.

3. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* **175**:255 (Feb.) 1928.

there was an average fall in T wave amplitude in lead II of 0.8 mm., five cases showing an increase of from 0.4 to 1.5 mm. and five a decrease of from 1.5 to 3.3 mm. In each group the maximum change in the T wave was observed at the time of the maximum systolic blood pressure reading, and in each the average time required for the wave to return to its normal amplitude was a little less than two hours. The alterations in the T wave in leads I and III were not significantly different from those in lead II. The changes observed in the curves of the two control groups agree in general with those recorded by Clough⁴

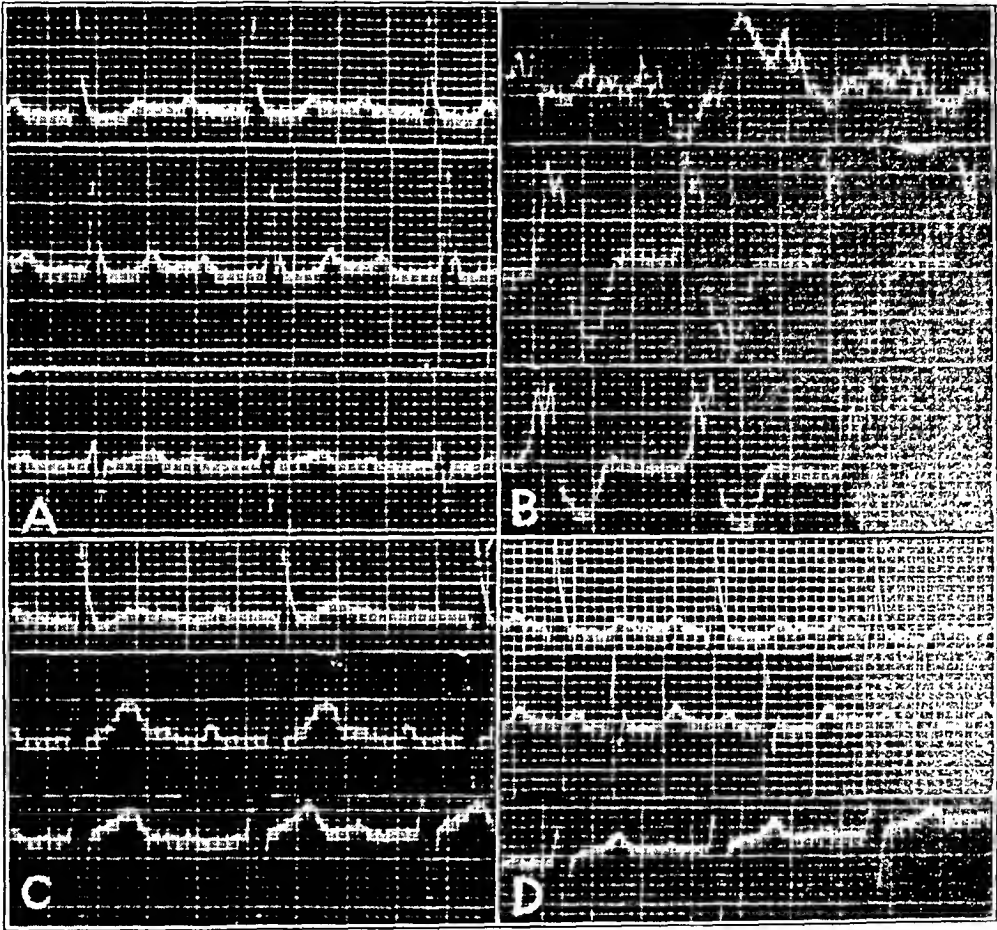


Fig. 1.—Electrocardiograms of patient, M. S., with angina pectoris. The customary three leads are shown in all figures with one-fifth and one-twenty-fifth seconds indicated. *A*, control record showing delayed A-V conduction; *B*, record at onset of pain, showing ventricular tachycardia; *C*, record two minutes after *B*, pain subsiding, showing return to delayed A-V conduction with T waves of increased amplitude; *D*, record seventeen minutes after *C*, showing return of T waves to original amplitude.

in normal soldiers and in soldiers with "irritable heart" after doses of 0.5 cc. of epinephrine.

4. Clough, H. D.: Studies on Epinephrin: III. Effect of Epinephrin on the Electrocardiograms of Patients with "Irritable Heart," *Arch. Int. Med.* 24:284 (Sept.) 1919.

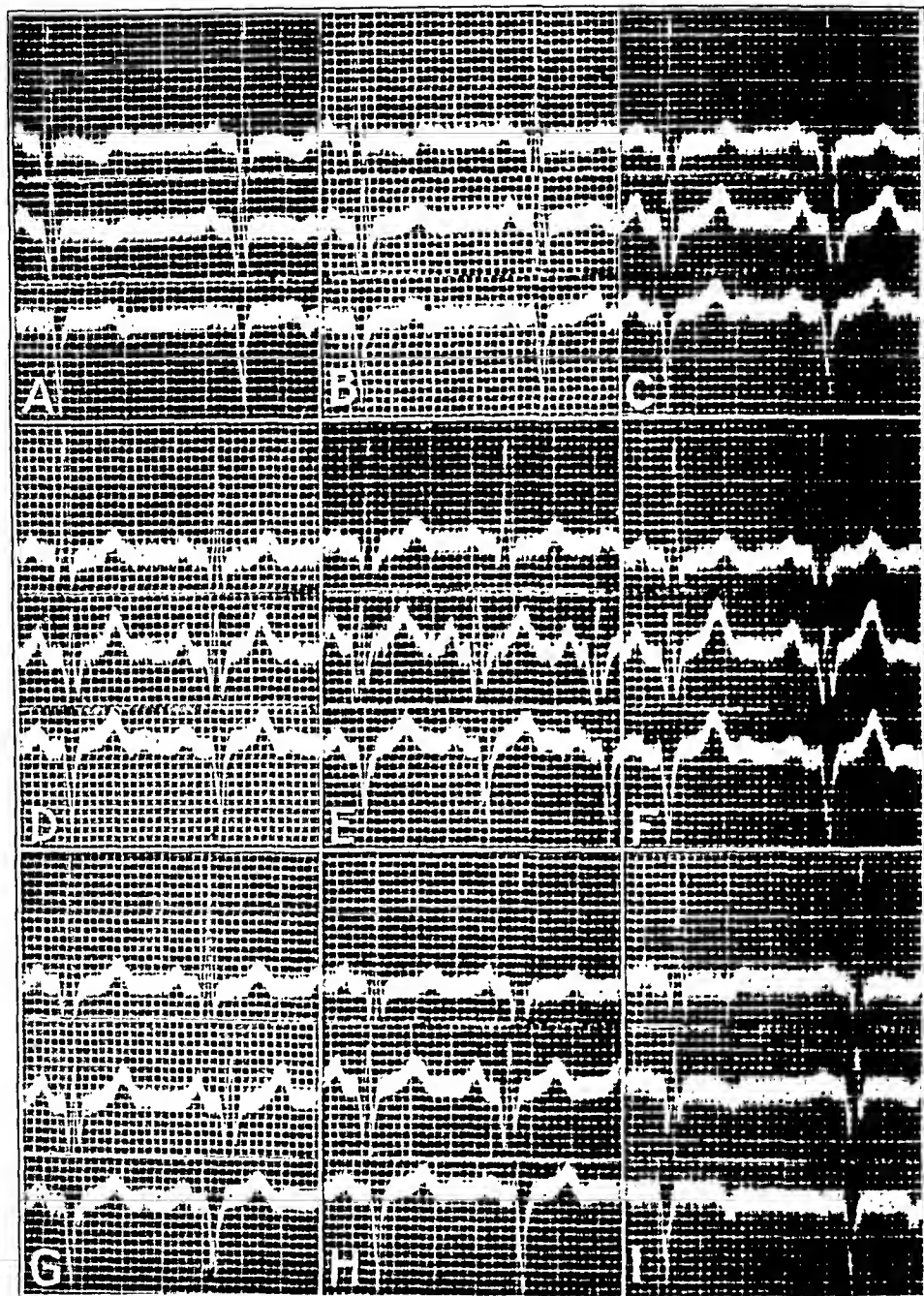


Fig. 2.—Electrocardiograms of patient, S. G., with angina pectoris, showing progressive increase in amplitude of T waves after the injection of epinephrine, with subsequent return to normal. *A*, control record, blood pressure 135 systolic and 72 diastolic; *B*, fifteen minutes after injection of epinephrine, blood pressure 142 systolic and 68 diastolic; *C*, twenty-one minutes after injection of epinephrine, blood pressure 178 systolic and 68 diastolic; *D*, twenty-eight minutes after administration of epinephrine, at onset of anginal pain, blood pressure 200 systolic and 80 diastolic; *E*, three minutes after *D*, blood pressure 210 systolic and 84 diastolic, pain severe; nitroglycerin $\frac{1}{100}$ grain (0.00065 Gm.) administered at end of this record; *F*, four minutes after *E*, blood pressure 190 systolic and 78 diastolic, pain diminishing; *G*, ten minutes later, at end of pain, blood pressure 144 systolic and 70 diastolic; *H* and *I*, at thirty minute intervals after *G*, showing return to original T wave amplitudes as the blood pressure dropped to 122 systolic and 68 diastolic.

COMMENT

The pathogenesis of angina pectoris is still obscure. The theory of Keefer and Resnik,⁵ however, that anginal pain arises as the result of anoxemia of a restricted part of the myocardium seems the most satisfactory of the many explanations offered to date. Epinephrine increases the amount of work which the heart is called on to perform as a result of the elevation of blood pressure and the increase in metabolism. It also increases the coronary blood flow. The former effect probably is more marked than the latter. In normal patients the increased oxygen

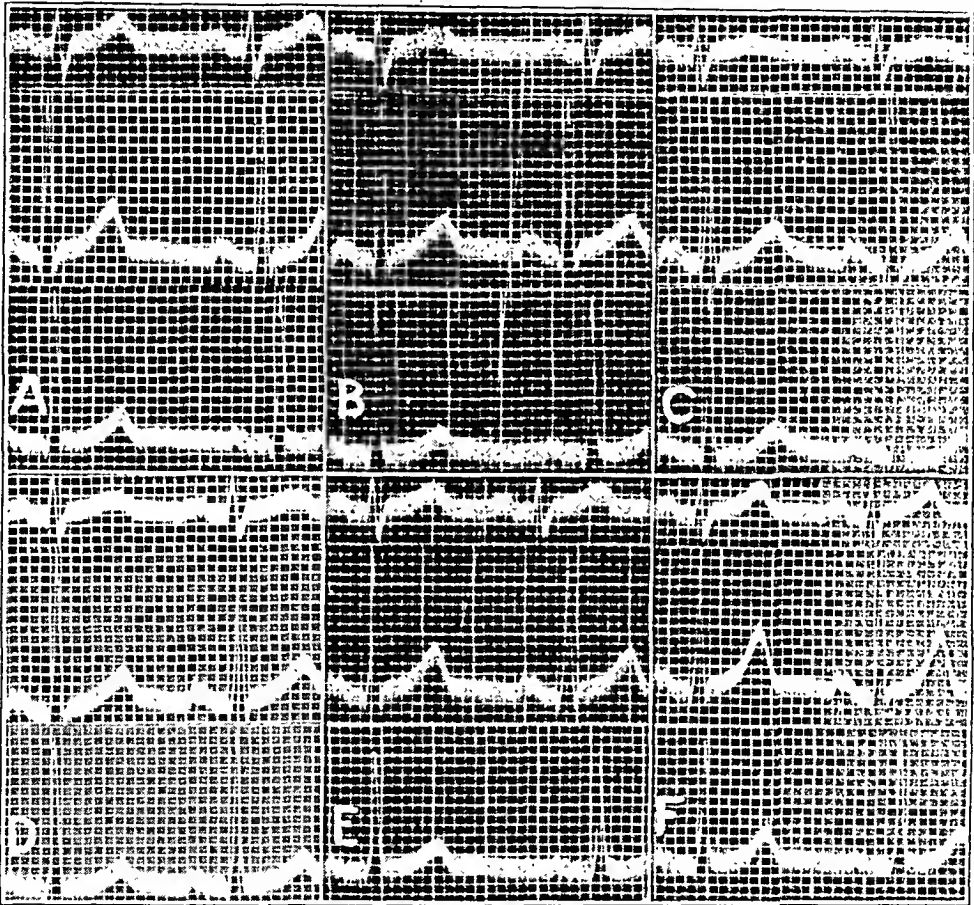


Fig. 3.—Electrocardiograms of young adult subject, B. J., showing slight decrease in amplitude of T waves with subsequent return to normal. *A*, control tracing, blood pressure 114 systolic and 66 diastolic; *C*, record at height of epinephrine effect, twenty-seven minutes after injection, blood pressure 146 systolic and 60 diastolic; *D*, one hour after *C*, blood pressure 122 systolic and 66 diastolic; *E*, one hour after *D*, blood pressure 116 systolic and 70 diastolic; *F*, one hour after *E*, blood pressure 114 systolic and 70 diastolic.

requirement of the myocardium after the administration of epinephrine may or may not be compensated for completely by increased coronary

5. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, *Arch. Int. Med.* **41**:769 (June) 1928.

blood flow. When, for any reason, the coronary blood flow is already below normal, it is logical to suppose that following injections of epinephrine a definite disproportion between the increased work of the heart and the available supply of oxygen will develop. If this is true, the occurrence of localized anoxemia of the myocardium after the injection of epinephrine into patients predisposed to such an occurrence by coronary artery disease (the probable underlying pathology in all our patients with angina pectoris) or by aortic regurgitation is easily understood. Assuming, therefore, that anginal pain is due to localized anoxemia of the myocardium, a rational explanation of the results obtained in the present study is available.

Anginal attacks are, of course, never without danger. Because epinephrine has now been shown to produce typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution. This may apply likewise to the use of ephedrine. When the diagnosis of angina pectoris is certain, there is no indication for the use of epinephrine as a diagnostic measure. Occasionally, however, patients are seen in whom, as pointed out previously, the diagnosis is doubtful; in such cases information as to the presence or absence of angina may be of the utmost importance.

CONCLUSIONS

1. Epinephrine was administered subcutaneously in doses of 1 cc. to three groups of persons: one group of eleven with angina pectoris, a second of ten of the same average age but without angina, and a third of ten normal young adults. In all but one patient with angina pectoris, typical pain resulted from the injection. In none of the control patients did this pain occur.

2. Electrocardiographic studies showed that following the injection of epinephrine the T wave in the anginal group increased slightly in amplitude, while in the other two groups it showed a tendency to decrease.

3. The increase in blood pressure and pulse rate was somewhat greater in the anginal group than in the others.

4. It is suggested that the production of anginal pain by the injection of epinephrine may serve as a diagnostic test for angina pectoris. The test would not be applicable when the diagnosis is certain but rather in doubtful cases or when there are other possible explanations for the symptoms, such as gallstones or disease of the stomach or the duodenum.

5. Because epinephrine produces typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution.

THE CAPILLARY CIRCULATION IN THE ALVEOLUS PULMONALIS OF THE LIVING DOG*

D. M. OLKON, M.D.
AND
MINAS JOANNIDES, M.D.
CHICAGO

In a previous paper¹ reporting the results of a capillaroscopic study of the pulmonary alveolus in the living dog, the capillary blood supply was merely mentioned. In this subsequent report, it is our purpose to describe the capillary circulation in detail.

METHODS AND RESULTS

It was stated in the previous report that the normal pleura may be regarded as a glass window through which one can study the structure and activity of the alveolus and its capillaries without disturbing the normal activity of these tissues.

Our observations were made by means of a Zeiss capillary microscope which was devised by Otfried Muller.² This microscope has a magnification of 60 and has a 6 volt lamp inside the tube of the microscope. The advantage of this instrument over others is that the light is direct and as the focus is moved the light moves with it so that the degree of illumination does not vary. Only a small amount of heat is given off by this lamp, so that no appreciable vasodilatation is noticed. Cedar oil or glycerin was spread over the field of observation, which gave a clearer vision.

Healthy dogs were used. The animal, which was quieted with scopolamine hydrobromide and ether analgesia, was studied with reference to its normal respiration, pulse and the skin capillaries. The lung was exposed by means of a thoracotomy incision, and the capillaries of the pleura and the lung were carefully observed before any changes were instituted. Two types of capillaries were seen, namely, the multicellular and the single cell. The term multicellular capillary is used for one in which the lumen is wide enough to permit more than one row of erythrocytes to pass through at the same time. A single cell capillary

* Submitted for publication, June 29, 1929.

* From the Departments of Neurology and Surgery, University of Illinois College of Medicine.

1. Olkon, D. M., and Joannides, Minas: The Structure of the Alveolus Pulmonalis of the Living Dog, to be published.

2. Muller, Otfried: Die Kapillaren der Menschlichen Korperoberflache in gesunden und Kranken Tagen, Stuttgart, Ferdinand Enke, 1922.

is one in which the lumen is wide enough to permit only one row of erythrocytes to pass in a single file.

Surrounding the alveolus there is a multicellular capillary (figs. 1 and 2). This gives off one cell capillaries at given distances. These smaller capillaries are usually arranged at right angles to the multicellular capillary but may sprout out at any angle. Depending on the degree of contraction or expansion of the air units, one can see a variable number of single cell capillaries. When the alveolus is expanded, a smaller number of single-celled capillaries is seen. On the other hand, when

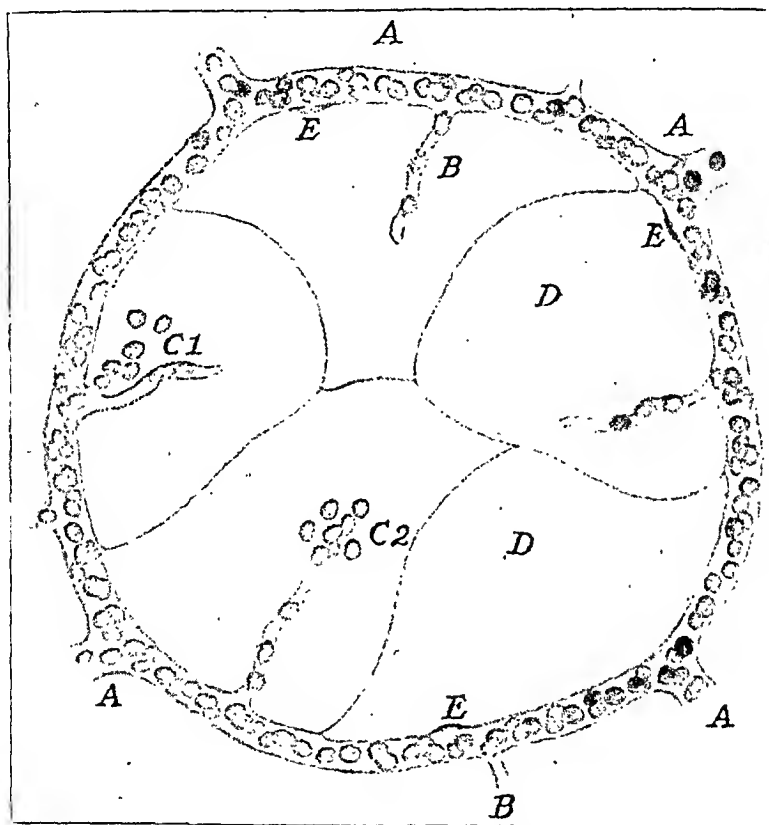


Fig. 1.—Diagram of alveolus and air units, showing capillaries in various states. *A* indicates a large multicelled capillary; *B*, a single cell capillary; *C*₁, a capillary rupture at the point of origin with liberated erythrocytes near the point of rupture; *C*₂, a single cell capillary ruptured at its distal end with liberated erythrocytes at that point; *D*, air spaces, and *E*, endothelial nuclei of the multicellular capillary.

the alveolus is contracted, a larger number of these capillaries can be seen.

When the intrapulmonic air pressure is increased so that the lung becomes distended up to a volume greater than the chest cavity, the single cell capillaries become thinned out and only a small number remain visible. As the distention of the lung is decreased, these capillaries again gradually become visible.

The flow of blood through the capillaries was greatly increased when the lung was distended to a volume greater than normal. Coincidentally, the one cell capillaries assumed a straighter outline and a deeper color. Likewise when the pressure was suddenly reduced, the flow in the larger capillaries assumed a to-and-fro movement, stopping for a moment and then moving again.

When the alveolus was overdistended with air, the capillaries showed changes in pattern in that they expanded and assumed a fusiform shape. These returned to their original tubular form when the alveolus contracted back to the usual size. Moreover, at the distal end of the single cell capillaries and also at the point of origin, free floating erythrocytes were seen, indicating that some of these small capillaries ruptured at these points because of the increased alveolar distention. In some of the single cell capillaries, a contraction was noticed in the middle half. This

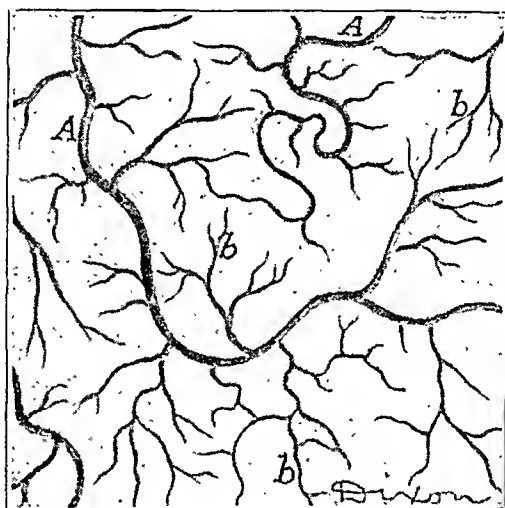


Fig. 2.—Diagram of capillary bed in the pia-arachnoid, showing normal arrangement of the capillaries. *A* indicates a normal large capillary of the pia-arachnoid in the living dog, and *b*, single cell capillaries given off principally at right angles.

contraction left a few erythrocytes immobilized close to the point where the capillary dips into the alveolus, assuming the picture of stasis (fig. 3).

Although these changes in the capillaries appear to be intimately associated with changes in the size of the alveolus, we believe that the capillaries per se may act independently of alveolar changes. In a study of the cerebral capillaries it was found that when the dog received a sufficient dose of strychnine to induce convulsions, the single cell capillaries seemed first to contract as the rigor appeared. During the convulsion they were almost obliterated from view (fig. 3). When the convulsions stopped, there was a state of intermittent contraction and dilation of the capillaries, and at this time hemorrhages appeared at points similar to those of the capillaries in and about the alveolus (fig. 1). In view of the fact that the cerebrum was exposed and there

was no increase of intracranial pressure because the dura was incised, it is safe to assume that these changes in the capillaries have occurred by changes in their tonus (fig. 3 *c*). Further evidence as to the presence of a tonus in even the smallest capillaries has been the effect of increased muscular activity on the alveolar capillaries. The changes in the alveolar capillaries that were noticed by hyperventilation of the lungs were also noticed when rigor was substituted. The activity of the capillaries in the lung is similar to that of capillaries elsewhere in the body. When changes occurred in the capillaries of the skin and the brain, under given conditions, similar changes were also noticed in the alveolar capillaries. Thus during the stage of excitement when the animal struggled the

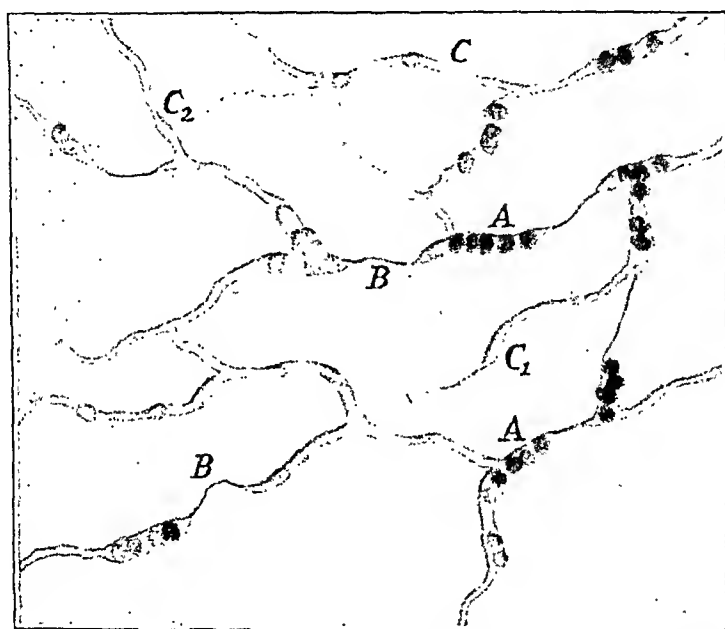


Fig. 3.—Diagram of capillary bed of the pia-arachnoid, showing changes similar to those of the lung capillaries. *A* indicates a portion of the capillary in which the erythrocytes are immobilized following spasm in a single cell capillary; *B*, a portion of the capillary showing spastic contraction; *C*, a portion of the capillary showing atony after contraction; *C*₁, a dilated portion of the capillary following spasm, empty of erythrocytes; *C*₂, a partial contraction of the capillary, empty of erythrocytes. *C*, *C*₁ and *C*₂ show the slowness of the capillary recovery to their physiologic norm after injury (time: from two to five minutes). (Primary hemorrhages almost always take place in these smallest units of the vascular tree and not formerly described in fixed tissue studies.)

superficial capillaries showed massive hemorrhages. Similar hemorrhages were also noticed in the capillaries of the lungs, liver, kidney, bladder and intestine. It would seem, therefore, that a study of the superficial capillaries is a good index of activity in the capillaries of other organs such as the brain, stomach, intestine, lungs, kidneys and bladder.

CONCLUSIONS

1. The capillary blood supply of the alveolus pulmonalis appears to be unique, and there seems to be an intimate relation between the changes of air migration in the alveolus and its capillary blood supply.

2. The finding of capillary changes in and about the alveolus suggests a probable index to changes which are at times symptomatic without gross clinical observations in the lungs.

3. The outstanding capillary changes observed were: contraction of the capillaries, rupture of the right angle single cell capillaries and microscopic hemorrhages in the immediate vicinity.

4. Mild trauma, such as hyperventilation or increased muscular contraction, gives rise to capillary hemorrhages heretofore not described in the histologic studies of fixed tissues.

5. The study of the superficial capillaries may be considered a good index of the earliest visible changes occurring in the capillary blood supply in organs of living animals under increased activity.

310 South Michigan Avenue.

3750 Broadway.

HEAT AND EFFORT SENSITIVENESS COLD SENSITIVENESS

RELATIONSHIP TO HEAT PROSTRATION, EFFORT SYNDROME, ASTHMA,
URTICARIA, DERMATOSES, NONINFECTIOUS CORYZA
AND INFECTIONS *

W. W. DUKE, M.D.
KANSAS CITY, MO.

In this paper I shall enumerate a series of relatively common illnesses, many of them serious, which are caused, rather frequently, I believe, by a disorder in the heat regulating mechanism. The illnesses include heat prostration, symptoms of effort syndrome, noninfectious coryza, asthma, urticaria, dermatoses and other miscellaneous ailments to be mentioned. They are commonly diagnosed neurasthenia, psychasthenia, allergy, atopy, vagotonia and eczema. The patients are hypersusceptible to infection during their reaction to heat or cold, especially infection in the nasorespiratory tract, and for this reason, their disorders are often classed with the infections.

HEAT REGULATING MECHANISM

Whatever the heat regulating mechanism may be, and wherever it may be, certain it is that it is an important and effective mechanism. It is important because it makes the difference between warm-blooded and cold-blooded animals. It is effective because it maintains body temperature at a relatively constant level in the normal person whether he resides at the equator or in the polar regions and whether he generates an enormous amount of heat through effort, or whether he is at rest or asleep.

Investigation of the heat regulating mechanism has interested many eminent physiologists, including Claude Bernard, Richet,¹ Cannon² and others. Many interesting facts of fundamental importance have been disclosed which should interest pathologists and physicians, especially those whose work brings them in contact with disorders commonly classified as allergy or atrophy, and with the so-called neuroses and the dermatoses.

Body temperature is kept normal and constant through the automatic control of heat generation and of heat loss. The automatic con-

* Submitted for publication, Sept. 4, 1929.

* Read before the Association for Research in Nervous and Mental Diseases, Dec. 28, 1928.

1. Richet, C.: *Chaleur dictionnaire de physiologie*, 1898, vol. 3, p. 178.

2. Cannon, W. B., et al.: *Am. J. Physiol.* 61:528, 1927.

trol is grossly strengthened by voluntary actions of a person when he feels too hot or too cold. Whereas the automatic and voluntary control of heat generation is grossly important, it is not so effective, I believe, under average conditions as the automatic control of heat loss. Both mechanisms, however, are important.

Overheating.—Heat generation is increased in a given organ by increase in its activity, whether the organ is the brain, a gland or a muscle. If excess heat thus generated is not adequately removed by increased blood flow, the organ is likely to become overheated and is likely to behave badly. An organ may be permanently damaged by overheating. The temperature at which an organ works to its best advantage is unfortunately dangerously near a temperature that is damaging to its function, so that prompt removal of heat from an active organ ranks in importance, I believe, with the prompt removal of waste products. Hyperemia is looked on as useful for carrying additional food and oxygen to an organ during periods of activity, and for the removal of carbon dioxide and other waste products. The probability is that it is equally useful for the prompt carrying away of heat. In fact, it might be well to call heat a waste product in the same sense that Mendel in his lectures to students of physiology, calls heat a waste product.

These facts seem so obvious that they should hardly need discussion. However, it may be well to emphasize the gross importance of a slight excess of heat as a disturbing and dangerous element by quoting several interesting experiments. Moore and Oslund³ stated that the temperature of the scrotum is several degrees below the average temperature in the peritoneal cavity. By wrapping ram's scrotum in such a way as to cause a rise in scrotal temperature toward the temperature of the peritoneal cavity, the spermatozoa were made to disappear from the testicle almost completely within a few months. These observers believed that this phenomenon was due actually to a rise in temperature above the optimum for this tissue, and that the absence of spermatozoa in undescended testicles is due primarily to the fact that peritoneal temperature is above the optimum for the normal life of spermatozoa. Heymans⁴ stated that the brain is more sensitive to high temperature than other organs and that a brain temperature of from 42 to 43 C. is fatal for rabbits. Heymans and Heymans⁵ found that brain temperature exceeding from 45 to 46 C. in dogs caused death of the brain cells.

3. Moore, C. R., and Oslund, R.: *Am. J. Physiol.* **67**:575, 1924.

4. Heymans, J. F.: *Arch. internat. d. Pharmakol. e. d. Therap.* **25**:1, 1919.

5. Heymans, J. F., and Heymans, C.: *Ann. Soc. sc. de Bruxelles* **46**:294, 1926.

Storm van Leeuwen and van der Mode⁶ found that reflexes in the cat were most active at a temperature of 38 C., and were rendered less active by a rise in temperature above this point. Lowering of temperature to 35 C. had little effect on reflexes, but lowering below this point reduced them. All observers seemed to find that animals stood a lowering of temperature much better than a rise above the optimum.

The foregoing statements refer to overheating of individual organs. Activity of several organs gives rise to a general increase in body temperature under normal conditions, unless heat loss from the nose, bronchial tubes or skin can be adequately increased. Heat loss can be increased through dilatation of blood vessels leading to the three important cooling surfaces, the skin, the mucous membrane of the bronchial tree and the mucous membrane of the nose. Cooling is aided by the secretion of moisture and evaporation from these surfaces, and by an increase in the depth and rapidity of respiration. If air is dry, evaporation is an important factor in the process of cooling. If air is saturated with moisture, the surfaces are cooled only by convection and conduction to the outside air. If outside air is moist, but cool, it may adequately cool the body. If, however, the outside air is moist and warm, heat loss is seriously retarded, and under these conditions, it is extremely easy for activity to cause overheating, illness and death.

Cerebral Heat Control.—Automatic control of body temperature is accomplished through the coordinated action of many structures that try to govern heat production and heat loss. Body temperature is regulated partly by a thermostat-like mechanism in the region of the thalamus. Barbour,⁷ Moore,⁸ Hashimoto⁹ and others demonstrated that by cooling an area in the region of the corpus striatum, rectal temperature can be increased, whereas by warming this same area, rectal temperature can be reduced. Isenschmid and Krehl¹⁰ demonstrated that the power to resist external changes in temperature without variation in body temperature is lost in animals if the midbrain is sectioned just anterior to the center of the optic thalamus. Experimental injury to the optic thalamus in pigeons caused them to lose their power

6. Storm van Leeuwen, W., and Van der Mode, M.: Arch. f. d. ges. Physiol. **165**:37, 1916.

7. Barbour, H. G.: Physiol. Rev. **1**:295, 1918; Arch. f. exper. Path. u. Pharmakol. **70**:1, 1912; J. Pharmakol. & Exper. Therap. **14**:65, 1919; Antipyretics: III. Acetylsalicylic Acid and Heat Regulation in Fever Cases, Arch. Int. Med. **24**:624 (Dec.) 1919; Am. J. Physiol. **55**:295, 1921; *ibid.* **67**:366, 1924.

8. Moore, L. M.: Am. J. Physiol. **46**:244, 1918; *ibid.* **1**:102, 1919.

9. Hashimoto, M.: Arch. f. exper. Path. u. Pharmakol. **68**:370, 1915.

10. Isenschmid, R., and Krehl, L.: Arch. f. exper. Path. u. Pharmakol. **70**:1 and 109, 1912.

to resist changes in external temperature (Rogers).¹¹ Resection of the stellate ganglion had the same effect (Freund).¹² Such experiments harmonize well with clinical knowledge. Diseases of the brain caused by hemorrhage, tumor, meningitis or trauma are likely to be associated with rapid oscillations in body temperature. There should be little doubt concerning the existence of automatic control of temperature by brain centers.

Endocrine Heat Control.—Several of the glands of internal secretion, especially the suprarenal, thyroid and pituitary glands, play rôles in the control of temperature. The effect of hyperthyroidism and hypothyroidism on the metabolic rate is so well known as to need no discussion. When the metabolic rate is abnormal in a case of dysthyroidism, the altered rate of heat production is often compensated for by an altered rate of heat loss, so that body temperature is not correspondingly altered. The suprarenal gland has an effect both on the rate of heat production and on that of heat loss, the former through modifying the metabolic rate, the latter through an effect on vascular tone and therefore on blood flow to cooling surfaces. Boothby and Sandiford¹³ reviewed the literature on the subject of the suprarenal gland in relationship to heat production, and confirmed the results of other observers in showing that the injection of epinephrine hydrochloride into animals even in physiologic doses noticeably increases the rate of heat production. Aub, Forman and Bright¹⁴ found that removal of the suprarenal glands was followed by a drop of about 25 per cent in the metabolic rate, even though the temperature of the body remained the same. McIver and Bright¹⁵ found that direct or reflex stimulation of suprarenal secretion promptly augments metabolism, often as much as 50 per cent. Cannon, Querido, Britton and Bright¹⁶ found evidence of an effect of suprarenal secretion on the heart rate in animals exposed to a cold environment or following the introduction of cold water into the stomach. This cold reaction could be stopped by application of heat. In animals in which one of the suprarenal glands was denervated, and the other removed, the heart rate was not effected by cold. Furthermore, they demonstrated an increase in metabolic rate in normal sub-

11. Rogers, F. T.: Relation of Cerebral Hemispheres to Arterial Blood Pressure and Body Temperature Regulation; Preliminary Note, *Arch. Neurol. & Psychiat.* **4**:148 (Aug.) 1920; *Am. J. Physiol.* **49**:271, 1919.

12. Freund, H.: *Arch. f. exper. Path. u. Pharmacol.* **46**:236, 1911; *ibid.* **72**:295, 1913; *Handb. d. norm. u. path. Physiol.* **17**:86, 1926.

13. Boothby, W. M., and Sandiford, I.: *Am. J. Physiol.* **66**:93, 1923.

14. Aub, J. C.; Forman, J., and Bright, E. M.: *Am. J. Physiol.* **55**:293, 1921; **61**:326, 1922.

15. McIver, M. A., and Bright, E. M.: *Am. J. Physiol.* **68**:622, 1924.

16. Cannon, W. B.; Querido, A.; Britton, S. W., and Bright, E. M.: *Am. J. Physiol.* **79**:1, 1927.

jects after the introduction of cold water into the stomach through a tube. If cold applications were gross enough to cause shivering, the rise in metabolic rate frequently amounted to as much as 50 to 90 per cent above the basal rate. They concluded that the same conditions that increase the suprarenal secretion in animals increase the metabolic rate in man, and that "a disturbing heat loss evokes activity of the adrenal medulla and that the output of adrenin by hastening combustion, serves to protect the organism against cold." They supported the contention of Voight and Ruebner that there exists in the body a mechanism for the chemical augmentation of metabolism. They believed that the secretion of the suprarenal gland is augmented by cold, and that this serves to increase the rate of heat production. Suprarenal secretion is believed to be governed both by the temperature of the blood and by sensory nerve impulses coming from the skin and other areas caused by heat or cold.

The pituitary hormones have a profound influence on growth and metabolism, but apparently little effect on heat production. This has been intensively studied clinically and experimentally, and negative or variable results have been obtained. Both suprarenal hormones and pituitary hormones, however, are interesting in relationship to heat loss, since the hormones of either gland have a profound influence on vascular tone. The intracutaneous injection of an extract of the suprarenal or pituitary gland in dilute solution causes vasoconstriction and capillary constriction with blanching of the tissues. There is some uncertainty as to whether or not there is an adequate quantity of epinephrine in normal blood to effect vascular tone. Krogh¹⁷ was inclined to believe that pituitary hormone is more important than epinephrine in this rôle—that is, as a normal regulator of capillary tone. Rehberg and Carrier¹⁸ found that extirpation of the pituitary gland caused loss of capillary tone in frogs, and Pohle¹⁹ found that its extirpation can lead to actual edema.

Histamine Effects.—The intracutaneous injection of a dilute solution of histamine causes local hyperemia, itching and edema—in fact, typical hives (Eustis²⁰ and others). Lewis²¹ recently emphasized the importance of histamine and allied bodies (which he called H-bodies) in relationship to vascular tone under physiologic conditions. His work

17. Krogh, A.: *Internat. Ztschr. f. phys. chem. Biol.* **1**:491, 1914; *J. Physiol.* **53**:399, 1919.

18. Rehberg, P. B., and Carrier, E. B.: *Skandin. Arch. f. Physiol.* **42**:250, 1922.

19. Pohle, E.: *Arch. f. d. ges. Physiol.* **182**:215, 1920.

20. Eustis, A.: *New Orleans M. & S. J.*, April, 1914, vol. 66.

21. Lewis, T.: *Heart* **11**:151, 1924; *Blood Vessels of Human Skin and Their Responses*, London, Shaw & Sons, 1927.

is based on a study of the blood vessels of the skin, but he inferred that the same influence may be exerted on other blood vessels, for example, those supplying muscle tissues. Histamine-like bodies are interesting in that they are liberated by putrefaction from protein foods and also by normal catabolic processes, and have been isolated from normal tissues. On injection histamine has an effect opposite to that of pituitary or epinephrine extract in that it causes capillary dilatation almost immediately. Lewis found that histamine has a more profound effect on capillary tone than pituitary or suprarenal extract because vessels that are dilated with histamine cannot be contracted with either pituitary or suprarenal extract even when used in relatively concentrated solution.

Pituitary hormone, suprarenal hormone and histamine-like bodies, therefore, working antagonistically and causing, respectively, vasoconstriction and vasodilation, must be looked on as possibly important factors in the regulation of blood supply and therefore important factors in the regulation of heat loss. As histamine-like bodies are liberated by normal metabolic processes, their influence in causing vasodilation and increased removal of heat cannot be overlooked as probably important factors in the regulation of the temperature both of active organs and of the body as a whole. This phase of the subject will be referred to subsequently in a clinical discussion.

Sensory Heat Control.—Whereas, in the previous paragraphs, emphasis has been laid on hidden mechanisms that effect heat production and heat loss, I would not lead the reader to infer that the more obvious factors are less important. For example, the sense organs for the perception of heat and cold have, no doubt, a rapid effect on both heat generation and heat loss, both automatic and voluntary. Richet¹ believed that reflexes from sensory nerves may cause the initial response to change of temperature. He noticed polypnea immediately after exposure of dogs to sunlight, even at a time when rectal temperature was temporarily falling. The fact is, that the application of heat to the skin in doses that could hardly cause any marked change in blood temperature may cause a quick change in the metabolic rate. Furthermore, the immediate effect of exercise on the respiratory rate is so obvious and gross as not to need experimental proof. It would be interesting to note whether or not there is a reduction in the tone of the muscles of the bronchioles and pulmonary vessels coincident with exercise which would aid in body cooling. This, one would think, should occur, but so far as I know, has not been experimentally proved.

Surface Temperature in Relation to Rectal Temperature.—Contrary to general belief, temperature is not the same in different parts of the body, nor is it constant in all localities under varying conditions of external temperature. For example, the temperature of the skin and

that of tissues immediately beneath the skin are grossly below rectal temperature. The average temperature of the skin, depending on the body covering, may vary from 24 to 34 C., and after exposure to cold, may fall grossly below this. The temperature of the skin and that of the muscles of the extremities are, as a rule, much below rectal temperature, and on exposure to cold, are reduced rapidly and to a surprising degree below rectal temperature. The temperature of the skin under the influence of exercise was studied by Benedict and Parmenter,²² who found that the average temperature of the skin is not increased, but is actually reduced one or more degrees by physical exercise in cold air, even though the metabolic rate may be increased as much as 500 per cent.

Whereas, under basal conditions about 75 per cent of body heat is lost by radiation from the skin, this is evidently not the case during periods of gross activity, when a large proportion of the excess heat must be lost by evaporation and convection from the respiratory tract. Apparently, constriction of surface blood vessels forces blood into internal channels during exercise, where it is used in supplying active tissues. It discharges the excess heat thus collected, through the pulmonary circulation into the respiratory tract. Whereas the respiratory tract may be a minor factor in body cooling during periods of rest, it becomes a gross factor during periods of high grade activity. The respiratory tract is a greater factor in heat removal in animals that do not sweat, such as dogs, than it is in man.

THEORY OF TEMPERATURE CONTROL

Richet's theory of the normal control of body temperature assumes that reflexes caused by the sensation of heat or cold on surface tissues give rise to prompt reactions that control body temperature under the usual conditions of living—that is, they modify heat production and heat loss so that body temperature remains the same. He believed that mechanisms affected by the temperature of the blood itself are less important, and play important parts only after considerable change in the temperature of the blood has occurred.

Bazett²³ combined the views of Richet, Meyer's theory of a dual heat center and the experimental work of Sherrington, and suggested the following hypothesis. The control of body temperature is almost entirely reflex, caused by sensory impulses from surfaces, caused by heat or cold. He believed that changes in blood temperature are effective chiefly through giving rise to a condition in the central nervous system that causes exaggerated responses to sensations of heat or cold.

22. Benedict, F. G., and Parmenter, H. S.: *Am. J. Physiol.* **87**:633, 1929.

23. Bazett, H. C.: *J. Physiol.* **36**:414, 1908; *Am. J. Physiol.* **70**:412, 1924; *Physiol. Rev.* **7**:531, 1927.

He assumes, for example, that a fall in temperature in the central nervous system gives exaggerated responses to the sense of cold, thereby, causing a warming of the body; whereas, a rise of temperature in the same area, gives exaggerated responses to the sense of warmth, leading to a general cooling of the body. In other words, the optimum brain temperature for reflexes giving rise to cooling and warming are not identical.

It is impossible in an article of this scope to do justice to the literature and investigations that have been made in this interesting field of work. I can only mention facts brought out by many investigators that show the importance and complexity of the heat regulating mechanism. Further discussion is beyond the scope of this article. What I wish most to emphasize are the facts that an abnormal rise in temperature in a given organ is damaging to the health and functional activity of the organ; that an abnormal rise of body temperature, in general, is damaging to the health and activity of the subject; and that there is a remarkably effective and complex mechanism which provides under normal conditions for the adequate cooling of both individual organs and the whole body. What I should like to draw attention to subsequently is that defective heat regulation may cause a variety of disorders affecting the body as a whole or affecting the functioning of one of the internal organs, and finally, and most startling of all, may cause abnormal responses in one of the three important cooling surfaces—that is, the skin and the mucous membranes of the nose and the bronchial tree and may cause in these localities serious pathologic changes.

The literature on the heat regulating mechanism was completely summarized in important papers by Barbour,⁷ Bazett,²³ and Cannon and his associates,² and to these the reader is referred for a detailed discussion of the subject.

FEVER

When the rate of heat production exceeds the rate of heat elimination, the temperature rises, and there is fever. Fever, as observed in the infectious diseases, is not always attributable chiefly to increased production of heat. It is caused often by reduced elimination of heat. This is evidently a fact, for the increased metabolic rates, such as are observed in malaria and typhoid fever, are not nearly so high as those observed with exercise or overeating. Furthermore, in some of the infectious diseases associated with fever, the metabolic rate is actually reduced.

It is stated in many of the textbooks on the practice of medicine and therapeutics, and probably correctly so, that in febrile conditions the heat regulating mechanism is working at an abnormally high level, so

that responses to a normal body temperature would simulate those normally caused by a reduced temperature, and give rise to a retention of heat. In harmony with this view, it is found that the skin of patients with fever is frequently hyperesthetic to cold. In the same way, one might account for the subnormal temperature so frequently observed during convalescence from febrile diseases by assuming that the heat regulating mechanism is then working at an abnormally low level so that normal temperature under these conditions would give rise to the responses normally caused by heat.

These points of view are interesting in relation to the discussion that is to follow, since I believe that many of the cases of so-called noninfectious coryza, bronchial asthma, urticaria and other dermatoses are caused by a defect in the heat regulating mechanism and frequently have their date of onset during or following an acute febrile disease. To account for the condition, one might assume that the usual level at which the heat regulating mechanism works during a period of fever or during a period of convalescence is maintained indefinitely or permanently and might cause the patient, thereafter, to be abnormally sensitive to the effect of heat or of cold or to the effect of both combined.

ACCLIMATION AND DECLIMATION

Healthy persons tolerate climates that vary tremendously in temperature of the air and moisture of the air. A rapid change in the location of sick persons from one extreme to another, however, may result seriously. Through gradual change, the same patients might become so acclimated as to tolerate the new conditions without gross ill effect. Races become so acclimated to extreme conditions that they live in comfort in atmospheres that prove injurious to newcomers. Persons visiting the tropics sweat much more than the natives. Vernon²⁴ noticed evidence of acclimation in experiments on muscular work in warm rooms. Bazett²³ noticed it in students kept in warm moist chambers for periods of one hour after ten or twelve exposures. Persons living in the temperate zones feel the effect of the first hot days of spring and early summer more than they do the hotter days of later summer. Likewise, they notice the effect of the first cold days of winter more than they do the colder days later in the season. Finally, persons who have been exposed for an hour or more to cold notice the effect of heat more than they do if they have not been thus exposed. Likewise, persons who have been exposed for an hour or more to heat notice the effect of cold more than they do if they have not been exposed to heat.

²⁴. Vernon, H. M.: *J. Physiol.* **17**:277, 1894; *Brit. M. Research Council Rep.* **73**:116, 1923.

These well known facts are referred to because under pathologic conditions, the behavior of a person under the influence of a change of temperature is so much more extreme than that referred to that it causes him to be ill enough to seek the advice of a physician. In these, the effect of acclimation or declimation may be much more marked. For example, certain patients with asthma or pruritus are declimated, or perhaps better expressed, unfitted for the cold days of winter by the prolonged summer heat. They may gain tolerance for cold during the winter months and tolerate it better. Others may be unfitted for the heat of summer by prolonged exposures to cold during the winter months. They may gain tolerance for heat or become acclimated during the summer months. In persons of this type, seasonal weather changes may have serious ill effects that are not noticed in normal persons. This will be referred to again subsequently.

MANIFESTATIONS OF HEAT AND COLD SENSITIVENESS

Certain persons through one or several causes become abnormally sensitive to heat or cold. This fact is so apparent as to need no discussion. Manifestations of sensitiveness to heat or cold are believed to vary depending on the primary cause of the sensitiveness and also on the direct inciting cause of the manifestation. Manifestations in some cases seem an exaggeration of a normal reaction to change of temperature or effort; in others, an inadequate reaction; in others, a pathologic deviation from a normal reaction; and finally, in some, an effort to compensate for a defect that prevents a normal response to change of temperature or effort.

Abnormal responses may be classified as follows:

1. General or constitutional reactions.
2. Reactions referable to one of three cooling surfaces; that is, the skin, the nasal mucous membrane and the bronchial mucous membrane.
3. Reactions referable to an internal organ.

Reactions of sensitiveness to heat or cold vary in intensity, in the quickness with which they appear and in location in different persons. In some patients, the reactions seem chiefly constitutional. Examples of this are heat prostration and the effort syndrome. In others, reactions may be referable chiefly to one of the cooling surfaces. Classic examples of this are thermic coryza, thermic asthma and thermic urticaria or eczema. In others, reactions may be referable chiefly to an organ. A classic example of this may be thermic headache or gastric upset caused by change of temperature or effort. The outstanding feature of all the disorders is that they can be consistently brought out, as the case may be, by heat or effort or cold, and can be temporarily relieved by the reverse condition—that is, in the cases of sensitiveness to

heat by cooling or inactivity, and in the cases of sensitiveness to cold by heat or effort.

Constitutional Manifestations of Sensitiveness to Heat; Relationship to Heat Prostration, the Effort Syndrome and Syncope.—Lewis' effort syndrome is frequently caused by sensitiveness to heat. Patients of this type after effort or exposure to hot, moist air often gave a history of exhaustion, weakness, dizziness, tremor, fainting spells or a tendency to faint, a feeling of oppression in the chest, palpitation, anorexia and nausea or vomiting. One or all of these manifestations may appear consistently as an effect of effort or overheating. Heat sensitive patients of this type are exhausted by effort, especially on hot, humid days. Heat, mental effort or physical effort may each have the same effect on highly sensitive persons. The reaction may be so marked that the patients are unable to tolerate the mental effort of watching athletic contests or of attending to an interesting business deal. Likewise, they may be unable to tolerate the physical effort of climbing up on an examining table quickly. Finally, they may be unable to tolerate as much heat as is encountered in the drinking of a cup of hot coffee or in the placing of their arms in a water bath of 42 C. for thirty seconds. In fact, I had one patient who lost consciousness under a heat test which was so mild that one would have to see before he could believe, and who recovered immediately when cooled by an ice rub on the arms.

The aforementioned triad of causative agents can be demonstrated in almost every case of high grade sensitiveness. In cases of moderate sensitiveness, the effect of the entire triad may not be so apparent. That is, the patient may be more sensitive to heat than to mental or physical effort, more sensitive to mental effort than to physical effort or heat, or more sensitive to physical effort than to mental effort or heat. The three agencies, however, can be demonstrated in a majority of cases of pronounced sensitiveness.

I feel certain that many cases of heat prostration and syncope are due to nothing more or less than heat sensitiveness. Patients who are highly sensitive to heat instinctively avoid heat and avoid effort on humid, hot days. If they are so unfortunate as to be unduly exposed to heat or forced to make an effort in hot, humid weather, they may faint, and in case the exposure is gross enough, may be actually shocked. Severe cases such as this may be diagnosed "sunstroke." An expression such as "overcome with heat" would seem more correct. The condition has nothing to do with the sun, except through heat produced by it. Patients rapidly recover from mild strokes of this kind if they are caused to remain quiet and if they are cooled by the removal of clothing, by an electric fan, or best of all, by the rubbing of the skin with ice.

The identity of the condition described and Lewis' effort syndrome should seem apparent. Lewis mentioned in his classic description of the

effort syndrome that symptoms are often brought to the surface through a change in habit such as that brought about by the drafting and drilling of men who had instinctively sought out sedentary lives. I have found classic examples of effort syndrome in persons who give a history of exhaustion, weakness, dizziness, breathlessness and tremor after effort, and who show exactly the same symptoms while absolutely quiet if they are heated with a hot lamp or a diathermic current, or if they immerse their hands and forearms in a water bath at 42 C. Likewise, their complaint can be immediately relieved by the cooling effect of an ice rub on the arms and chest. Furthermore, these patients can usually tolerate a moderate grade of effort if they are simultaneously cooled.

Lewis made the important observation in his study of the effort syndrome that in a large proportion of cases the symptoms followed an acute infectious disease. This, likewise, is true in my series of cases of heat sensitiveness. A large proportion of my patients who show no definite physical defect can definitely date the time of onset of their symptoms to a febrile disease.

A curious phenomenon can frequently be demonstrated in this type of sensitiveness. Symptoms can be elicited not only by immersing the hands and forearms in a water bath at 42 C., but can be incited in this way even after tourniquets have been applied around the arms above the elbow so tightly that blood can neither enter nor return from the arm. Strange to relate, symptoms brought out in this way can be caused to disappear almost immediately if the forearms are rubbed with ice even if the tourniquets have not been removed. Removal of the tourniquets before or after the application of ice does not materially add to the severity of or relief of their complaint. This observation has caused me to believe that symptoms in heat sensitive patients of this type are in part a response to a sensation of heat, and that the application of ice to the skin is an effective remedy, even though it could not directly lower body temperature. In one patient with urticaria who was so highly sensitive to heat that the immersing of one hand in a water bath at 42 C. would cause generalized erythema, pruritus and urticaria, the immersing of one hand in warm water and the other in cold would have no ill effect—that is, the effect of heat in one area could be immediately neutralized by cold in another area. Furthermore, the effect of heat produced by effort could also be prevented or immediately stopped by the effect of cold on the skin.

Symptoms Similar to Effort Syndrome Caused by Cold and Relieved by Heat.—The manifestations of cold sensitiveness may be identical with the aforementioned symptoms, except that the symptoms may be brought out by cold instead of by heat or effort. Patients of this sort are inclined to seek activity and when active enough, they are inclined to feel healthy. Exposure to cold, however, especially when they are

quiet, may cause symptoms such as exhaustion, weakness, dizziness, tremor, palpitation, oppression in the chest and nausea, and in addition, may cause symptoms referable to one of the cooling surfaces—that is, swellings of the mucous membrane of the nose and bronchial tubes or of the skin, or, in addition, may cause symptoms referable to disorder in one of the internal organs, such as headache or precordial pain.

Symptoms can often be reproduced objectively in persons sensitive to heat or cold by rubbing the skin with ice or by having them immerse their forearms and hands in a water bath at 15 C. In the latter case, symptoms often can be brought out by a cold application to the forearms even if tourniquets are tightly applied around both arms above the elbow. Release of the tourniquets may add little if any to their symptoms. Immersing the arms in warm water or the application of heat to the chest may give relief within a short time. These symptoms like the symptoms of heat sensitiveness seem to occur as a response to the sensation of cold and often can be neutralized by the sensation of heat in another locality.

Symptoms Referable to the Cooling Surfaces—i. e., the Nasal Mucous Membrane, the Bronchial Mucous Membrane and the Skin.—This class of disorders is important and widespread and may appear in heat sensitive persons under the influence of increased production of heat or reduced loss of heat, or in cold sensitive persons under the influence of reduced production of heat or increased loss of heat. They may also appear apparently as a result of a sensation of heat or cold. They can be brought out objectively in the same way in which the constitutional symptoms just described can be brought out—that is, by heat or effort, in heat sensitive patients, and by cold and inactivity in cold sensitive patients.

The nasal symptoms consist of sneezing and swelling of the membranes of the nose with increased secretion of clear mucus. If the condition is perennial and of years' standing, chronic edema of the membranes may lead to infection or polyps or both. If swelling is marked, it frequently causes headache.

The bronchial symptoms consist of a feeling of oppression in the chest, cough, and in the more marked cases bronchial obstruction giving rise to asthma. This is frequently accompanied with expectoration of clear mucus. If the condition is chronic, infection may be superimposed, giving rise to true bronchitis.

The skin symptoms may consist of erythema, itching, urticaria, angioneurotic edema, and if the condition is chronic, one or more of the following abnormalities: desquamation, increased secretion from the skin, thickening of the epidermis, cracking of the skin and occasionally herpetiform eruptions. In patients with chronic sensitiveness, especially in those who have prolonged, delayed reactions, the dermatoses may

assume grave and ugly proportions. Swelling, redness, desquamation, secretion and cracking can render the patient unsightly and most miserable. Infection may be superimposed, giving rise to multiple suppurations. There is one class of patients who have skin as dry as parchment. They never sweat nor can moisture be felt on the skin. One whom I observed had a dry parchment-like rash resembling ichthyosis which was made worse by heat or effort. Patients of this class may be the same as those described in the literature who show wide oscillations in body temperature and who do not sweat. The dermatoses caused by heat or cold sensitiveness may be generalized, may occur in patches or may be confined to the exposed parts. The conditions are diagnosed under a wide variety of terms.

Symptoms Referable to an Internal Organ.—These symptoms are almost too numerous to mention. They frequently appear as a result of the effect of heat or cold or effort. They may appear in persons who seem physically normal. There is in addition a class of patients in whom pathologic changes can be found. In these, symptoms may appear under strain. I believe this accounts for the rapid exhaustion of individual organs observed so frequently in older people with arteriosclerosis. As characteristic examples of this may be mentioned: profound mental exhaustion under the influence of emotional disturbances or mental effort; precordial pain and palpitation under the influence of a little effort; abdominal pain following a little effort; pain in the joints or in the muscles following effort, etc. In cold sensitive patients, the identical symptoms may be caused by cold and prolonged inactivity. These symptoms can often be reproduced under observation by the adequate application of heat or cold and can be relieved by the reverse application.

TYPES OF CASES—RELATIONSHIP TO ACCLIMATION AND DECLIMATION

Among thermic sensitive persons, there are those who are so highly sensitive to heat that the effort of getting up out of a chair quickly may precipitate an attack. Likewise, there are patients who are so highly sensitive to cold that the removal of clothing may precipitate an attack. There are, in addition, patients who are only moderately sensitive or slightly sensitive and who do not react unless considerably exposed. There are, furthermore, persons who have immediate reactions and respond within a few seconds or minutes after exposure, and persons who have delayed reactions. In the latter, the manifestations of the reaction may not appear for many minutes or even several hours after exposure. The latter type of person is unfortunate, for he is not so likely to observe a relationship between cause and effect, and is more likely, therefore, to expose himself unwittingly to extremes that he cannot tolerate. In other words, patients who react promptly are likely

to learn their limitations; whereas patients with delayed reactions frequently do not learn this, and frequently expose themselves to the point of causing a dangerous illness. This type of reaction may result fatally.

Under the topic of acclimation and declination, the effect of marked changes in temperature on average persons was reviewed. The behavior of many heat sensitive persons is similar to that of average persons, except that it may be much exaggerated. Certain thermically sensitive patients react perennially; others react seasonally. The mere fact that a patient is sensitive to heat does not mean that he is inclined to react only in summer. Also, the fact that he is sensitive to cold does not indicate that he reacts chiefly in winter. The fact is that among heat sensitive patients, one finds some who react perennially, others who react only on the hotter and more humid days of summer, and others who react to heat only after previous exposure to cold. If the latter are chilled, they react as they warm up. Others may react to the first

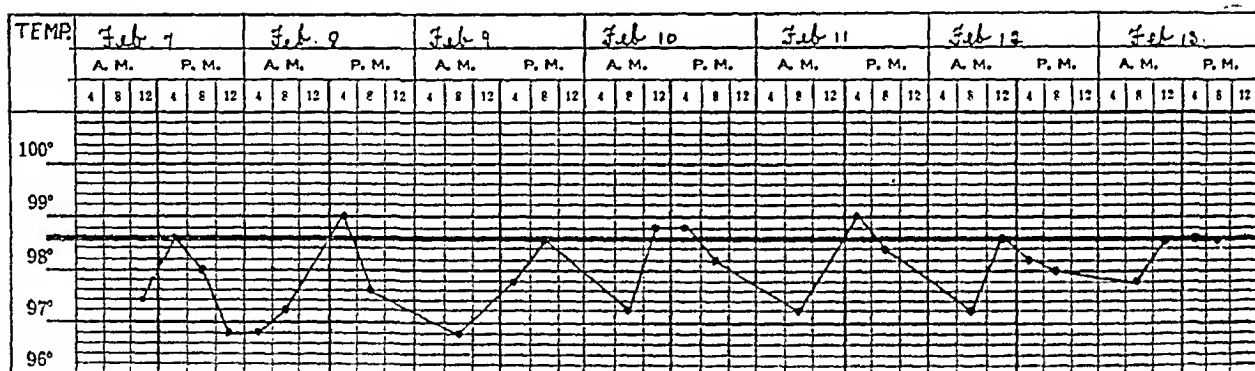


Fig. 1.—The temperature curve in a case of winter urticaria caused by sensitiveness to heat, especially after exposure to cold. Note the typical temperature curve running almost constantly subnormal. When the temperature was raised to normal or a little above by the repeated use of typhoid vaccine, the patient was clinically much better. His sensitiveness to heat, with its manifestation, urticaria, returned after the temperature again fell to its earlier subnormal levels. The basal metabolism was about normal.

warm days of spring after prolonged exposure to the cold of winter. During summer months, they seem to become acclimated to heat and gain tolerance, while during the winter months they become declimated, that is, lose their tolerance for heat. Finally, there is a type of heat sensitive person who reacts after the first cold days of fall or winter. This type seems to lose tolerance for heat under the influence of exposure to the first days of cold weather, and reacts during a warm spell following a cold spell. Likewise, among cold sensitive persons, there are those who react during the coldest days of winter. Some react chiefly in summer. They react to cold most markedly after exposure to heat. During the winter months, they seem to gain

tolerance for cold and cease reacting. In other words, they become acclimated and often tolerate cold better at the height of a winter season than they do at its beginning. They seem to become declimated for exposure to cold by the hot days of summer. Finally there are cold sensitive persons who react to cold chiefly after exposure to the first warm days of spring or summer. They are apparently declimated for cold by the first hot days.

These groups of patients whose reactions I believe are due to the effect of acclimation and declimation confuse the clinical picture and

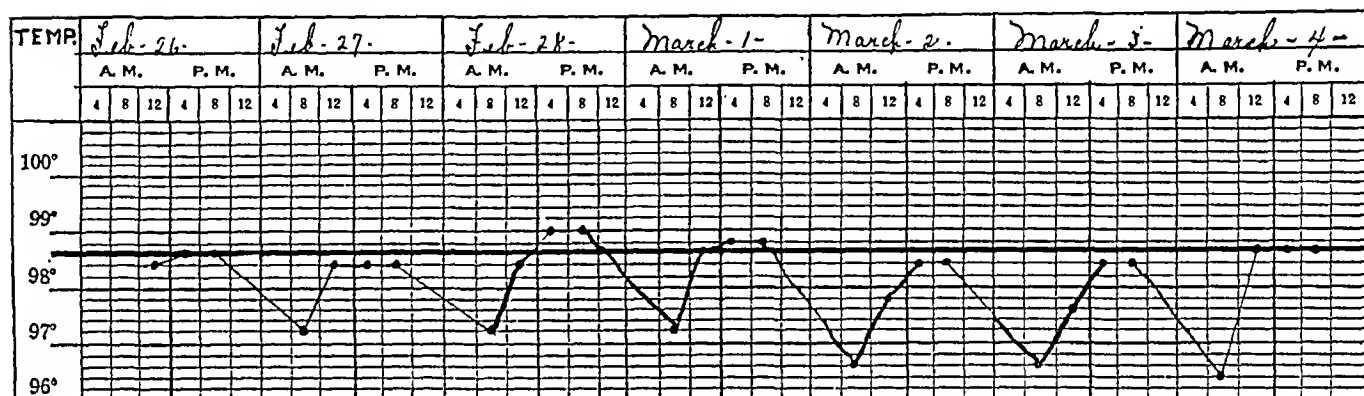


Figure 2

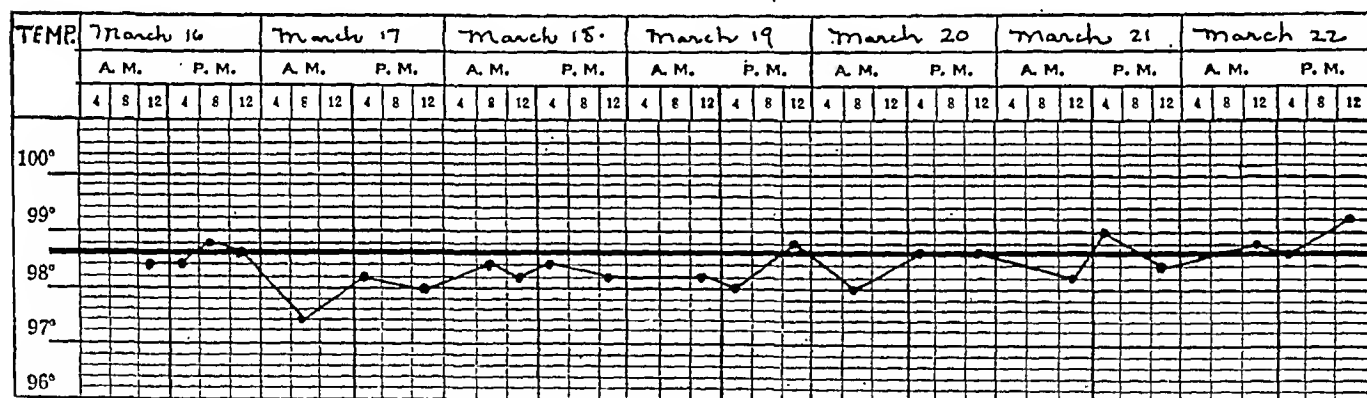


Figure 3

Figs. 2 and 3.—The temperature curves in a typical case of effort syndrome and summer urticaria. In figure 2, the temperature is shown almost constantly subnormal. During periods such as this, if the patient was subjected to heating with a nitrogen lamp or to heating of the forearms and hands with water at 42 C. or subjected herself to a little exertion, mental or physical, she reacted with prostration or an outbreak of urticaria or both. During periods such as that shown in figure 3, when the temperature was kept at a more nearly normal level, the patient could tolerate such degrees of heat as she encountered in her usual activities. The basal metabolism was about normal.

make the patients seem erratic in their behavior toward exposure to heat or cold or effort. The fact is, however, that these patients are extremely consistent in their reactions, in fact so consistent that they

only appear inconsistent. They can be understood after careful study and are then found to react consistently to the conditions of heat, cold or effort to which they happen to be sensitive.

Combined Sensitiveness to Heat and Cold.—The situation is further complicated by the fact that many patients react to body heat most markedly if simultaneously exposed to surface cold. Likewise, other types react to body cold most markedly when exposed to surface warmth, that is, warm, humid air. This condition is commonly observed and confuses the clinical picture. It makes the behavior of the patient seem inconsistent. The fact is, however, that the behavior of these patients also is absolutely consistent. If these patients are studied adequately, they are found to react to the temperature effect to which they are sensitive.

For example, certain asthmatic patients sensitive to heat and effort have reactions only when breathing cold air. They tolerate heat or effort better during the summer months than during the winter months. They tolerate effort better when indoors than when out of doors breathing cold air. A patient of this type may have asthma, if he sleeps in a cold room and uses an excess of cover. He may remain free from reaction if he sleeps in a warm room and uses little cover. In several cases this advice has sufficed to relieve persons with severe chronic asthma. Likewise, cold sensitive persons may tolerate body cold if they are breathing cold air, but may have asthma or a nasal reaction if they breath warm, moist air. Persons of this type are inclined to have attacks following cold baths in the summer. They may tolerate cold baths during the winter months. The cooling of the body by air currents may precipitate attacks if the patient is breathing air which is warm and moist. The patient may tolerate air currents easily, if he is breathing air which is cool and dry.

Whereas, these peculiarities of thermic cases may seem confusing and indefinite, the fact is that the reactions are extremely definite and confuse one only when one does not understand the peculiarities of the type of case under observation.

The reactions described can be reproduced objectively by the appropriate application of heat, cold and effort and can be relieved by a reverse application. This topic will be considered again subsequently.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO INFECTION

In the early part of this work, I quickly learned to my sorrow that in testing patients sensitive to heat and cold, I several times caused them to have febrile attacks that were diagnosed bronchitis or coryza, and in two cases, pneumonia. I quickly learned to be careful in testing patients sensitive to heat and cold and in case of reaction immediately to

reverse the application so as to relieve the condition promptly. Since I have followed this procedure, I have had no ill effects from testing.

These experiences caused me forcibly to realize that patients who are sensitive to heat and cold are more susceptible to infections on exposure to certain changes in temperature than are normal persons. In fact, patients who are sensitive to heat or cold are prone to have one or several febrile attacks each year, occurring usually with the changeable weather in the spring or fall. The reality of this susceptibility can be emphasized, perhaps, through mention of the expression of "catching cold." Normal persons can stand considerable exposure without "catching cold." Heat or cold sensitive persons can often stand little. Heat and cold sensitiveness of mild grade is frequently observed in elderly people, and it is for this reason, I believe, that they "catch cold" so easily on exposure to cold air currents, especially if they have been a little overheated. I think heat sensitiveness and cold sensitiveness are definite factors in the epidemiology of spring and fall colds and pneumonia. Heat sensitive and cold sensitive persons on adequate exposure to changes of weather are prone to become infected. Elderly persons often realize this instinctively, and carefully avoid exposures exceeding their tolerance. Young healthy persons can disregard this.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO ATOPY

The relationship of heat sensitiveness and cold sensitiveness to atopy is interesting. Both illnesses may have the same effect in causing so-called allergic coryza, asthma, dermatoses and allergic shock. When a person is specifically hypersensitive to an agent such as pollen or egg and is also heat or cold sensitive, his symptoms are naturally aggravated greatly if he reacts to the material agent and to heat and cold at the same time.

The reaction to foreign agents such as pollen or egg has, I believe, an unstabilizing effect on the heat regulating mechanism and causes the patient to react more readily to heat or to cold than he otherwise would. It has been found necessary, for example, to be much more careful in the injection of pollen in the treatment of hay-fever and asthma due to pollen, on hot humid days than when the weather is mild. A reaction to pollen is frequently brought to the surface by exercise and heat soon after the patient leaves the physician's office in a state of health. An ice rub applied to the chest and arms is an effective remedy for this type of reaction. In fact, this ranks in its therapeutic effect second only to epinephrine.

The fact that thermic sensitiveness and pollen sensitiveness may occur in the same person and that one of these conditions adds to the ill effect of the other might lead some to believe that the two conditions

are identical; that is, that thermic sensitiveness is caused by atopic sensitiveness. The fact is, however, that the two conditions seem more often distinct and separate. Whereas, both these types of sensitiveness may occur in the same person, this is apparently the exception rather than the rule. Whereas, pollen reactions and thermic reactions may occur simultaneously in a person, they frequently occur at different times of the year; that is, patients may have hay-fever or asthma due to pollen during the fall months and may have identical symptoms caused by thermic sensitiveness during the winter months, when the air is free from pollen.

RELATIONSHIP OF HEAT AND COLD SENSITIVENESS TO HISTAMINE-LIKE BODIES

Since the early writings of Eustis on histamine in relation to the etiology of asthma and urticaria, writers have been attracted by the idea that histamine, if absorbed from the intestinal tract or elaborated internally in excessive quantities, could cause the clinical manifestations of asthma and allied conditions, and they have endeavored to prove this. Since histamine-like bodies, if present in adequate quantities, can cause symptoms similar to those caused by egg in egg sensitive persons or by heat or cold in heat or cold sensitive persons, the simple deduction that egg, heat or cold in certain persons exerts its pathologic effect through the liberation of histamine would be most attractive and might prove correct. This could hardly seem a factor, however, in the patients previously referred to who were caused to react to heat or cold applications on the forearms while tourniquets above the elbow prevented a return of blood from the arm. It could easily be a factor, however, in adding to a reaction caused by egg sensitiveness or due to absorption of histamine because the three conditions give similar symptoms and two or three causes working simultaneously could have a more profound effect on a person than one cause acting alone. The part which might be played by histamine-like bodies in reactions of this type merits all the attention that it may attract. It has been studied recently by Thomas Lewis and by Harris Lewis and Vaughan.

ETIOLOGY AND PATHOGENESIS OF HEAT AND COLD SENSITIVENESS

The study on which this paper is based had been in progress for a number of years before any idea was gained concerning the probable pathogenesis of the condition. It was simply noted that the symptoms enumerated were caused in some patients by heat or effort and were relieved or prevented by cold or rest; while in other patients, the reverse status obtained—that is, identical symptoms were caused by cold or inactivity and could be prevented or relieved by heat or effort.

It was stated in my first communications on the subject²⁵ that it was believed that the symptoms were due to a disorder in the heat regulating mechanism; in other words, that the patients made a faulty effort to maintain ideal temperature under varying conditions of heat production and heat loss.

Primary Cases.—It has been noticed since then that a large proportion of the patients date the onset of their trouble from an acute febrile disease such as pneumonia, typhoid fever, tonsillar abscess, rheumatic fever or one of the diseases of childhood. This is particularly true of the younger patients, and in these, frequently no definite lesion of any sort can be found on most careful physical examination to account for the disorder, except the history of a febrile disease. I have heard patients say that there seems to be no outward manifestation that a doctor can discover which can account for what they feel within. Usually, such patients seem to be physically perfect, except for the fact that one group cannot stand heat or effort and the other group cannot stand cold or inactivity. They are, unfortunately, often condemned for their inability to carry a burden which they find placed on them.

Secondary Cases.—In a minority of the younger patients, and in many of the older ones who are sensitive to heat or cold, organic lesions can be found which could theoretically play a part in upsetting the normal behavior of the heat regulating mechanism and which might account for their disorders, such, for example, as organic diseases in the nervous system, endocrine disorders, arterial disease, anemia, debilitating diseases, senility or convalescence from a febrile disease. Patients of this class are more likely to receive kindly consideration from their physicians and families.

There are several points at which one could look for disease which might affect the activity of the heat regulating mechanism and cause it to behave badly.

1. In the sense organs and afferent nerve mechanisms which convey the sense of heat or cold to higher centers.

2. In centers in the brain or cord or elsewhere which act as thermostatic regulators of temperature.

3. In the complicated nerve mechanisms that carry efferent impulses from nerve centers which control the caliber of vessels supplying active organs and cooling surfaces; which modify the depth and rapidity of respiration; which control the secretion of moisture on cooling surfaces; also, those that carry impulses which affect the metabolic rate or cause shivering and which might cause one voluntarily to be more active or more quiet and to seek increased or reduced heat loss.

25. Duke, W. W.: Allergy, St. Louis, C. V. Mosby Company, 1925; Urticaria Caused by Light, J. A. M. A. **80**:1835 (June 23) 1923; Urticaria Caused Specifically by Action of Physical Agents (Light, Cold, Heat, Freezing, Burns, Mechanical Irritation, and Physical and Mental Exertion), *ibid.* **83**:3 (July 5) 1924; Physical Allergy; Preliminary Report, *ibid.* **84**:736 (March 7) 1925.

4. In end-organs (such as blood vessels, active tissues, surface tissues and secreting structures) which take part in heat regulation.

5. In glands of internal secretion which furnish substances that directly affect metabolic rate and that can also directly affect the caliber of vessels.

6. In the presence of abnormal amounts of histamine-like bodies, which can have an effect similar to that of pollen in pollen sensitive patients or egg in egg sensitive patients and cause reactions similar to those described as caused by heat or cold.

7. Finally, in debilitating diseases, such as anemia, cardiac or renal disease, postfebrile conditions or senility, which weaken the organism as a whole and in this way indirectly interfere with the normal responses to heat or cold.

This series of points at which one might look for trouble is broad in scope. The heat regulating mechanism, however, is exceedingly complex and depends on the coordinated action of many widely separated structures for its effectiveness. A breakdown at any point might alter its normal behavior and cause trouble. Changes at any of these points might theoretically interfere with the normal responses to heat and cold, and through this cause illness. It must be repeated, however, that in a great majority of the younger patients who are highly sensitive to heat and cold, no abnormality can be found to account for the condition except the history of a febrile disease; therefore, one must be satisfied, in many instances, with saying that the heat regulating mechanism is apparently disordered and reacts excessively, inadequately or pervertedly in its response to changes of temperature. I believe the clinical symptoms in the skin and in the nasal and bronchial membranes and, perhaps, elsewhere are due more often to a spasmodic and defective response to change of temperature than to a direct effect of such a change per se on the tissues. The pathogenesis, in this respect, is, I believe, analogous to that of a condition such as cirrhosis of the liver, in which defective efforts at repair do more harm than the primary injury.

EXPERIMENTAL HEAT SENSITIVENESS

I have been able to render tadpoles and minnows sensitive to heat by injuring them with the x-rays. In two series of experiments, each repeated a number of times, a little in excess of an erythema dose of the x-rays was administered to groups of tadpoles and to groups of minnows in shallow dishes of water. After a period of about two weeks, they were tested by placing them in beakers of water and gradually raising the temperature of the water until they were killed. Both the irradiated tadpoles and the irradiated minnows showed little difference in activity as compared with normal controls tested similarly with the rise in temperature until approximately 35 C. was reached. Above this level or thereabouts, each degree of rise had a more pronounced effect on the irradiated animals than on the untreated controls. The treated tadpoles and minnows almost without exception showed disturbed move-

ments or began swimming on their backs or died at a temperature of from 1 to 3 degrees lower than that which affected the controls. Both irradiated and untreated animals were handled identically and at the same time. Reducing the temperature nearly to the freezing point showed less or no difference in the behavior of treated and untreated specimens.

It was concluded that the x-rays so injure young tadpoles and minnows that they cannot adjust themselves so well to a rise in temperature above 35 C. as can the normal, untreated controls.

These experiments were a poor imitation of heat sensitiveness as observed clinically. In the experiments, heat per se apparently did the damage. In the clinical cases, however, the reaction to heat apparently does the harm. The rise of temperature per se is too trivial to account for the profound results that follow an increase in heat or effort.

CLINICAL EVIDENCE OF DISORDER IN THE HEAT REGULATING MECHANISM

Evidence of disorder in the heat regulating mechanism displayed by patients who are sensitive to the effect of heat cold or effort may be summarized as follows:

1. *Unstable Temperature.*—The patients almost always have an unstable temperature. Instead of varying as it does in the average normal person around 98.6 F., with the morning temperature slightly below the evening temperature and with relatively slight change under the influence of the average effort or exposure to heat or cold, the temperature is usually subnormal and frequently is almost constantly subnormal and varies grossly in a majority of cases under the effect of altered heat production or altered heat loss. In the average mild case, the temperature runs between 96.4 and 98 F. Frequently, the temperature almost never reaches normal, and frequently the morning temperature falls as low as 96 or even 95 F. In one extreme case of heat sensitiveness, the morning temperature was occasionally found as low as 92 F. In these patients, a change in temperature of 1 or 2 degrees up or down can often be caused by surprisingly small amounts of effort or by the application of heat or cold to the skin. If the temperature is abnormally low, a hot bath, the application of a hot lamp or the immersion of the forearms in water at 42 C. frequently causes a rise in temperature of from 1 to 2 or more degrees. Conversely, rubbing the chest or arms with ice or immersing the forearms in a water bath at 15 C. for from one to five minutes may cause a drop or occasionally a rise in temperature of 1 or several degrees. These observations have been made a great many times on over 100 heat sensitive or cold sensitive patients, and are remarkably constant. Because of varying degrees of heat production and heat loss encountered in the daily routine of

life in many patients, the variation in temperature is highly variable and erratic—in fact, the temperature curve compares well in irregularities with that in the case of ulcerative endocarditis, except that instead of the irregular, erratic febrile curve of endocarditis, one finds an erratic, irregular subnormal curve. Whereas a subnormal temperature is the rule in heat and cold sensitive patients, some of the latter (cold sensitive ones) run a normal or slightly elevated temperature which is less variable than that found in the heat sensitive patients. For the heat sensitive patients, a subnormal, variable and unstable temperature curve is almost constant, except at odd intervals when they may have febrile attacks. During febrile attacks, they may be very ill, although relieved temporarily of their reactivity to heat. Frequently, agents that stabilize the temperature and keep it up give marked clinical relief to the patient. For example, asthma caused by heat sensitiveness is almost always relieved during the febrile period of an infectious disease even by the fever caused by pneumonia and in one case by a lung abscess.

2. *Basal Metabolism.*—The basal metabolism is not so easy to study as the body temperature, and in the majority of cases I was unable to demonstrate consistent changes that I could be sure were outside normal variation. However, in a few cases, I demonstrated high grade abnormality and instability in metabolism. In a few cases, the metabolic rate was as unstable as the temperature. I have found it as low as from -40 to -58 on several consecutive days in a patient who seemed physically perfect, except for attacks of itching and urticaria which could be brought out by effort or heat. In one patient, metabolism could be brought up to a normal rate within a few minutes through the effect of a little effort or by the application of a little heat to the skin. It may be said in passing that the outbreaks of hives in this case were believed to be the automatic erratic effort to compensate for the lowered metabolic rate and change of temperature. When the rate was brought to normal, the patient was clinically relieved from urticaria.

It is occasionally observed that the metabolic rate is abnormally high and can be reduced by the application of cold to the skin. Strange to relate, a reduced rate frequently rises after the application of cold to the skin. In many cases, heat and cold may have the same effect so far as change in the metabolic rate is concerned. In some cases, the metabolic rate seems unusually unstable, reacting with ups and downs to a greater extent than it does in normal persons.

Often with a highly pathologic metabolic rate, the temperature may be nearly normal, and vice versa with a markedly subnormal temperature, metabolism may fall within normal limits.

The metabolic rate is not so simple a matter for study in this as it is in thyroid disease. In fact, because of its instability and variability,

I was inclined in my earlier work to believe that the metabolic rate was a minor factor or that I was making frequent errors in my estimations of the rate. This earlier deduction may or may not be correct.

Unfortunately for this study, heat sensitive patients frequently have their pathologic symptoms between midnight and 8 a. m., and at these hours one rarely has the opportunity of studying metabolic rates. Also, frequently when the patients have symptoms, such as asthma, it is not possible because of the nature of the illness to obtain the metabolic rate satisfactorially. Occasionally, I have observed patients with asthma subject to several attacks daily in whom the attack would invariably continue until there was a definite rise or a definite fall in rectal temperature. It would be grossly interesting to know what metabolic change, if any, occurred with this change in symptoms and change in temperature. Such determinations, however, are almost impossible to obtain,

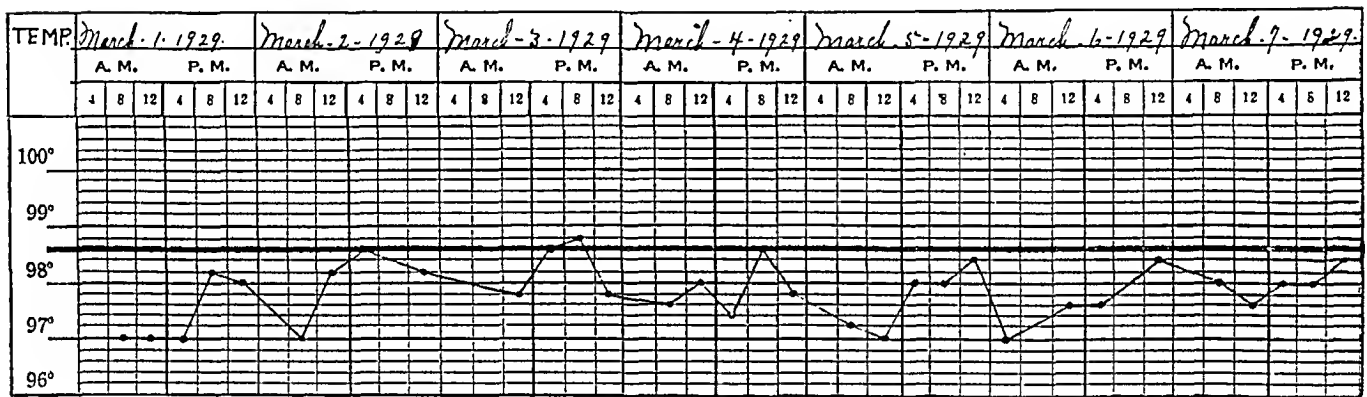


Fig. 4.—The temperature curve of a patient with urticaria of four months' standing caused by sensitiveness to heat. The eruption could be brought out immediately through the effect of heat or effort. This patient, contrary to the rule, showed an endocrine disorder characterized by abnormal length of legs and arms and a metabolic rate that on repeated examination was grossly below normal. On four nearly successive days, it gave such results as -42 , -56 , -46 and -62 . After heating the arms and hands by immersing them in water at 42 C. for five minutes and after heating by a nitrogen lamp applied to the chest for a few minutes, metabolism could be raised nearly to normal—on one occasion from -56 to $+16$. On one occasion, after an ice rub, from -31 to -4 ; and on another occasion, from -62 to -9 . With the use of glandular extracts designed to raise metabolism, tests a short time after the starting of treatment gave such results as -9 , $+19$, $+9$ and $+19$. This was associated with gross clinical relief. Note the irregular, unstable subnormal temperature shown here. There was a total absence of signs of myxedema to account for this patient's lowered metabolic rate.

because the patients during attacks are often so ill that even to get the temperature of the mouth is difficult.

3. *Hyperesthesia to Heat or Cold.*—A number of patients who react abnormally to heat or cold have skin hyperesthesia to heat or cold.

Occasionally, the application of a degree of heat that would scarcely feel more than warm to a normal person feels to these patients as if it might burn or blister. Or, in the case of cold hyperesthesia, an application that might scarcely cause discomfort to the normal person feels so cold to the hyperesthetic patient as to cause him to shudder. A rather large proportion of heat or cold sensitive patients are hyperesthetic to heat or to cold and because of this, instinctively avoid undue exposure.

4. *Reproduction of Symptoms by Application of Heat or Cold and Prevention or Relief by a Reversal of Application.*—The views expressed in this paper are not based on statements made by patients who say that symptoms are brought out by heat or cold, but are based on the fact that the symptoms of which they complain can be reproduced under suitable conditions by the application of heat or cold, and can be relieved by the reverse application. The study is based on a study of patients who were highly sensitive and who reacted immediately. In these, under suitable conditions, the symptoms of which the patient complained could often be elicited and relieved at will by heat, cold or effort. A study of this sort cannot be made on mildly sensitive patients or on patients who give delayed reactions, because of the fact that in these, the results are not sufficiently outspoken to be convincing.

In patients who are highly sensitive to heat, symptoms can be reproduced not only through the application of heat in the form of hot packs, a steam room, a hot lamp, autocondensation current or a diathermic current, but through the effect of heat generated by mental effort or physical effort. In highly sensitive patients, mental or physical effort and heat may give identical results, although in some the maximum effect is produced by one or the other of these three agencies. For example, one of the most highly sensitive patients whom I have examined, could be thrown into an attack of superficial urticaria by the application of a nitrogen lamp to the arm for thirty seconds, by the drinking of a cup of warm water, by heating electric currents, by the effort of leaning over and straightening up several times or by mental effort such as can be elicited by an interesting business deal or by watching an athletic contest. These reactions could be immediately stopped or prevented by the simultaneous application of cold, such as by the air from an electric fan, or by placing the hands in cold water, or by rubbing the arms with ice or by having the patient keep motionless for a time. In other patients highly sensitive to heat, in whom the clinical manifestation was effort syndrome, bronchial asthma or coryza, attacks of effort syndrome, asthma or coryza, as the case may have been, could be brought out by similar applications.

In cold sensitive patients, the reverse status obtained. The patients were benefited instead of made ill by heat or effort. In certain cold

sensitive cases, for example, urticaria could be brought out by immersing the forearms in cold water. In others, asthma or nasal reactions could be brought out through the same agency. The reactions could be relieved or prevented by the application of heat or through effort. Patients of this type feel their best during periods of high grade activity and when warm.

BEHAVIOR OF PATIENTS SENSITIVE TO HEAT AND COLD

Sensitiveness to heat or cold has an interesting effect on the behavior of the afflicted persons. Heat sensitive persons instinctively try to avoid heat and effort. They seek sedentary lives and quiet. They may give the appearance of laziness and may get rattled and hopelessly incompetent when hurried or hot. Cold sensitive persons, on the other hand, may be the reverse, seeking activity both in their business lives and in their games. It is not rare to find cold sensitiveness in highly active, energetic people. I have observed three cases of this sort in polo players. Such patients are completely rid of their troubles during the excitement and effort of a polo game and may have recurrences of symptoms between periods and when they cool off.

It is unfortunate for a patient to change a status in life that he has instinctively chosen and found compatible with his make-up. For example, during the war, many heat sensitive men were drafted and on being drilled in the hot sun, collapsed. In many instances, unfortunately, they were believed to be shirking their duties because on examination nothing could be found to account for their collapse. Lewis relieved this situation greatly by his classic description of the effort syndrome.

Cold sensitive persons who have instinctively chosen a life of activity are unfortunate if necessity forces them into environments where they are cold or inactive for prolonged periods of time. This was notably the case in a patient who was forced into prolonged inactivity by the illness of her husband. The illness that she had when I saw her had actually become more serious and more disagreeable than that suffered by her husband. She obtained immediate relief when she was caused to resume her previous life of activity. I might guess that Napoleon was cold sensitive. It could account for his life of excessive activity, his failures during periods of inactivity and his frequent prolonged hot baths. Frequent cold baths would have been disagreeable for him but more beneficial ultimately. Through this agency he might have gained a very useful tolerance for cold.

Heat sensitive persons often move slowly and methodically, and do things well if allowed time, but collapse or fail if hurried. On the other hand, cold sensitive persons may work best when pressed for time, and often fall down badly if the work before them is not lively enough to keep them adequately active.

THE TERMS HEAT SENSITIVENESS AND COLD SENSITIVENESS

I have used terms in this discussion which can be rather loosely used and which do not commit one to a theory. I do not believe at this stage in the development of this study that stricter terms or restricted definitions can be used. It seems evident that in persons who are sensitive to the effect of heat, cold or effort there are a number of different underlying pathologic conditions that give rise to identical clinical manifestations.

In this paper, therefore, I have employed the terms about as follows: "Heat sensitiveness" has referred to patients who were apparently made ill by an increase in body heat whether this was produced through reduced heat loss, external addition of heat or the generation of heat by mental or physical effort. Patients who responded to increased heat and effort most markedly after previous exposure to cold were considered, in spite of this history, as heat sensitive. Also, persons who responded most readily to heat or effort when breathing cold air were referred to as heat sensitive.

"Cold sensitiveness" was used in referring to patients who were made ill by body cold whether produced by increased loss of body heat or through reduced production of heat as the result of mental or physical inactivity. Cold sensitive persons occasionally reacted most markedly in a hot environment; that is, on cooling off after exposure to heat. These appeared, nevertheless, to be made ill by the immediate effect of cold and were therefore classed as cold sensitive. Furthermore, patients sensitive to the effect of body cold who reacted most markedly while breathing warm, moist air, were called cold sensitive.

In view of the fact that some heat sensitive persons react after previous exposure to cold and that some cold sensitive persons react most markedly after previous exposure to heat, and that many react most markedly to internal heat if subjected to surface cooling and vice versa to internal cold if subjected to surface heat, it might seem simplest in a large proportion of cases to refer to the condition as combined sensitiveness or to refer to the condition under the still less committal term "thermic sensitiveness."

DIAGNOSIS

The diagnosis of thermic sensitiveness is not difficult if one is acquainted with the subject matter described in this paper. The history is important, that is, a history of symptoms such as those mentioned which are brought out by heat or effort or which are brought out by cold or inactivity, and which tend to be relieved by the opposite states. Patients can be tested with heat, cold and effort so that their symptoms can be reproduced during well periods directly under observation. This tends to make the diagnosis objective.

After an impression of a case is gained by history, an effort can be made to reproduce symptoms in heat sensitive cases by immersing the hands and forearms in a water bath at 42 C., or by the application of the heat of a large nitrogen lamp to the chest and arms or by diathermic currents. In case of suspected cold sensitiveness, an effort can be made to reproduce symptoms by having the patient immerse his arms and hands in a water bath at 15 C. or through rubbing his arms and chest with ice.

If these applications are not adequate to reproduce symptoms, further tests can be made in heat sensitive patients by trying simultaneously the effect of heat and physical exercise or by placing the patient in a steam room and having him exercise.

For the testing of combined sensitiveness to heat and cold, a hot lamp can be applied to the chest and simultaneously a large pack filled with cracked ice can be applied to the face in such a way that chilled air can be inhaled. If this application is inadequate, an effort can be made to reproduce symptoms by having the patient exert himself physically while in a refrigerator breathing chilled air. The reverse application is easier to apply—that is, the rubbing of the chest, arms and back with ice while the patient is breathing air through a warm moist pack on the face.

If symptoms are reproduced by one of these applications, relief can usually be obtained in a short time by reversal of the application.

These tests can cause coryza, bronchitis or pneumonia if applied too severely. This complication can be prevented if reactions are stopped immediately by reversing the application that caused reaction.

TREATMENT

The treatment of patients highly sensitive to body heat and effort is likely to be a serious problem. The treatment of patients sensitive to body cold is likely to be brilliant or at least successful.

Treatment of Persons Sensitive to Heat.—Patients who are highly sensitive to heat should avoid effort unless they can be adequately cooled. They should avoid situations in which they are likely to be overheated. They are likely to do best in a dry, cool climate. Even a dry, warm climate may be better for them than a cool, humid climate. Dry air makes body cooling easier. Heat sensitive patients can stand more effort in a dry atmosphere than they can in a humid atmosphere. It may be necessary for them to seek an environment and career that will enable them to lead a quiet life in a dry atmosphere. This may be the best solution in cases of extreme sensitiveness.

In cases of moderate sensitiveness, relief can frequently be obtained through attention to the general health and through the use of agents designed to keep body temperature running at a higher level. Common sense practice of medicine is useful in the less severe cases. Since a

large proportion of the patients react most markedly when the body temperature is lowest, the avoidance of high grade subnormality in temperature is important. Many of the patients are definitely benefited through the effect of fever. A febrile disease almost always gives temporary relief and frequently prolonged relief. Fever can be given artificially through the subcutaneous or intravenous injection of colon bacilli. Through the use of this with gradually increasing doses carried on for a period of one or several weeks and increased to the point of giving frequent febrile reactions, I have been able to effect clinical relief

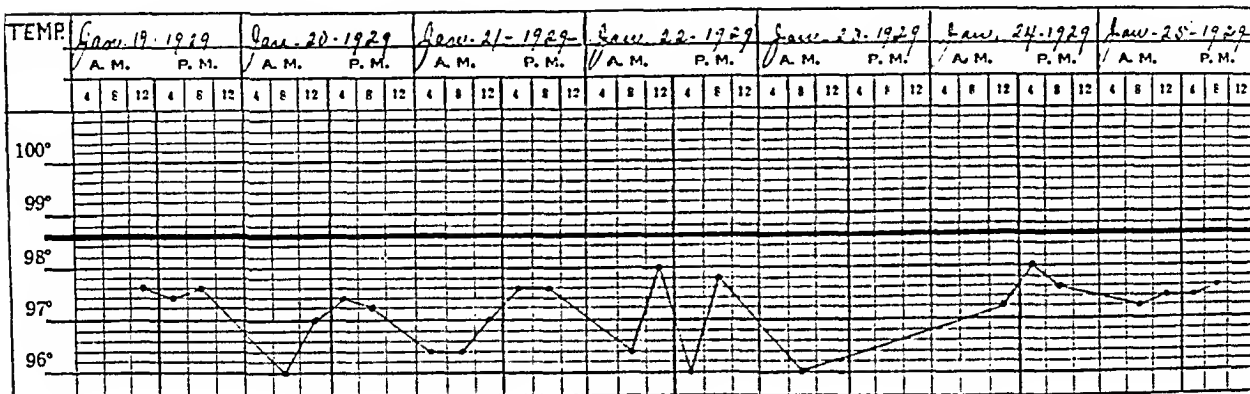


Figure 5

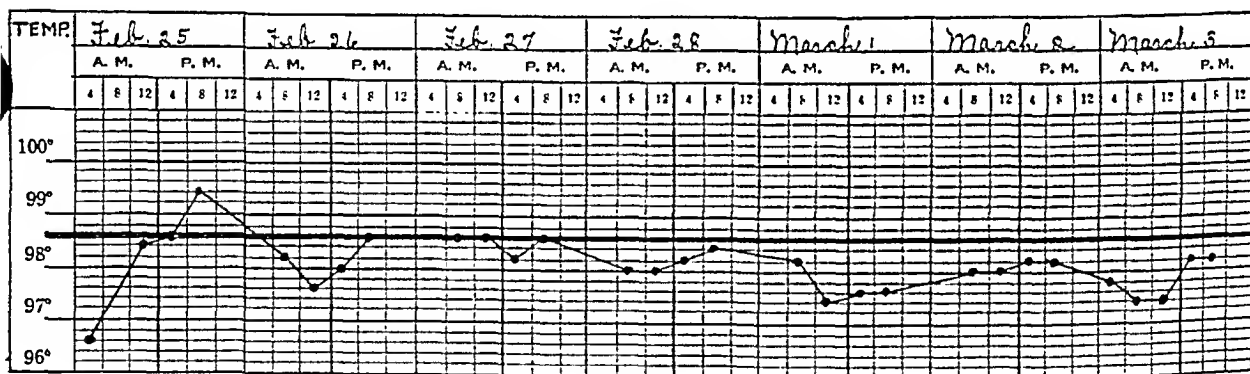


Figure 6

Figs. 5 and 6.—The temperature curves in a case of generalized seborrheic dermatitis present summer and winter without remission for several years, caused apparently by sensitiveness to heat. Note in figure 5 that the temperature curve was almost constantly subnormal. This was typical of the periods in which the eruption was active. Through heat or effort, the patient could be made definitely worse. With the use of heroic doses of *Bacillus coli* designed to raise body temperature to a higher level and frequently above normal, the eczema completely disappeared. The resulting level of temperature is shown in figure 5. In figure 7, note the generalized dermatitis, photographed as darkness of the skin. This photograph was taken at a period when the temperature was running almost constantly subnormal and the eruption active. Note in figure 8 the lighter color and the reappearance of hair and eyebrows after relief from the condition, brought about, I believe, through elevation of the body temperature. The basal metabolism was relatively normal.

in several desperately afflicted patients who had been ill for a number of years. The intravenous use of colon bacilli is likely to give a quick febrile attack even if given in doses as small as 10,000. Although I have had no unfortunate results with this form of therapy, I think the subcutaneous use of colon bacilli is much safer. It has to be pushed boldly, however, for a successful result. I do not wish to recommend this arbitrary method of treatment too strongly, but I can frankly say that I believe some of the therapeutic results that follow the use of

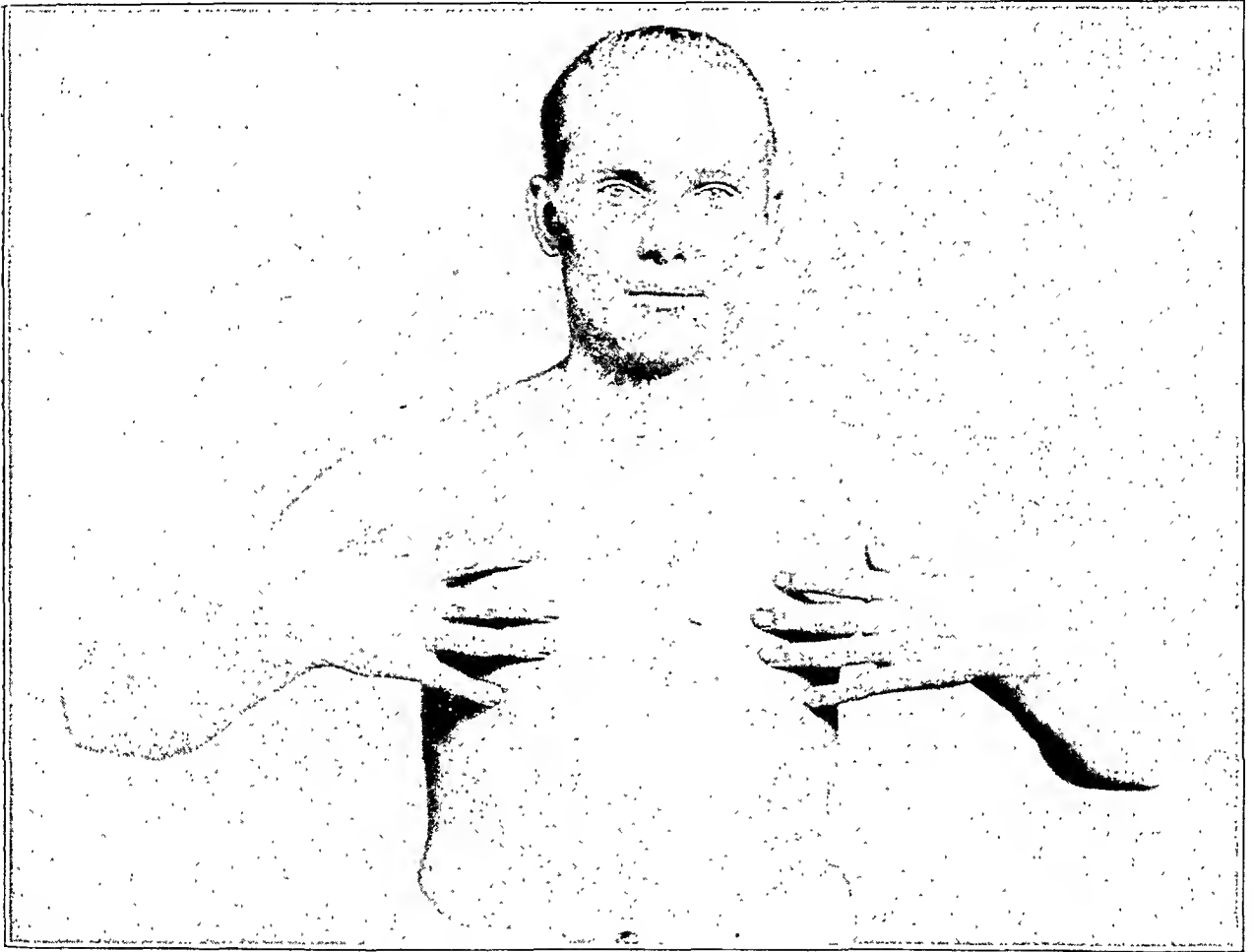


Fig. 7.—The patient with generalized seborrheic dermatitis referred to in figures 5 and 6. Note the pigmentation of the skin and the loss of hair and eyebrows. The patient had for several years been a victim of chronic scaly, weeping eruptions which had constantly resisted therapeutic measures.

autogenous vaccines, peptone and milk in the treatment of persons with noninfectious coryza, asthma, eczema and hives frequently owe their beneficial effect to the elevation of body temperature from subnormal toward normal or above normal.

Temporary relief can often be obtained through the use of hot or cold baths given when the patient needs them. Cold baths for the temporary relief of an attack may be effective within a few moments

and may give a sensational result. Hot baths at midnight for the prevention of a drop in temperature from relatively normal to high grade subnormality during the early morning hours may prevent attacks. I have several times been able to prevent early morning attacks through warming up the patient thoroughly by a hot bath at midnight.

Symptomatic remedies that are useful for symptoms such as coryza, asthma, urticaria and pruritus are epinephrine, pituitrin, ephedrine,

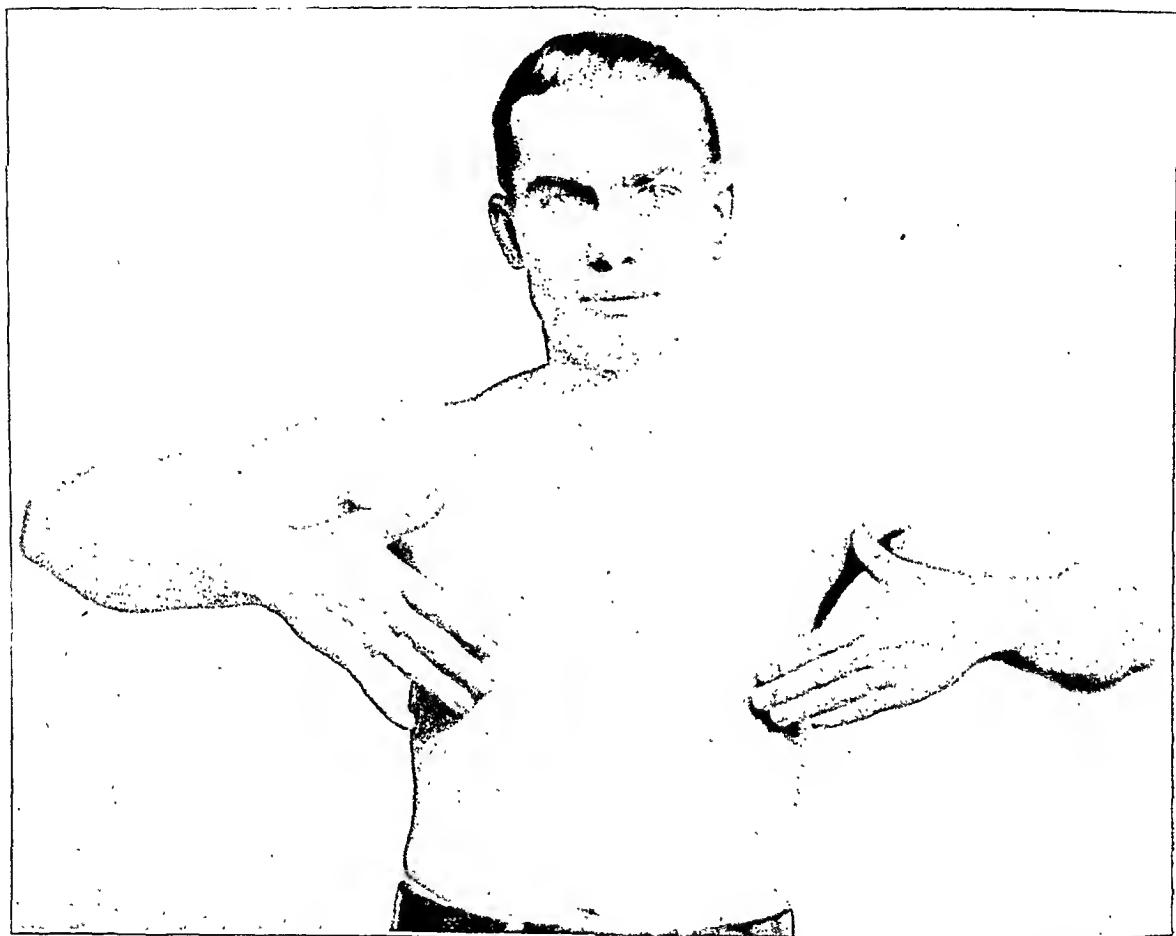


Fig. 8.—The patient shown in figure 7 after the use of therapeutic measures that elevated the body temperature toward normal or a little above.

atropine and the salicylates. Morphine and alcohol may be effective. The former is rarely justified. Acids are indicated if achylia is found.

Cold Sensitiveness.—Cold sensitive patients are much more fortunate than heat sensitive patients. In the first place, it is much easier to avoid overcooling than it is to avoid overheating. If a person is chilled, he can frequently relieve himself through exercise.

Cold sensitive patients, like heat sensitive patients, tolerate changes of temperature in a dry climate better than in a moist climate. Dry air,

whether hot or cold, is easier for them to tolerate than humid air. They should be cautioned against undue exposure to cold.

Fortunately, patients can frequently gain tolerance for cold through the use of frequent cold baths. This is often a most useful remedy in a proved case of cold sensitiveness. Frequently, one can effect complete clinical relief in a cold sensitive patient through so simple a measure as having the patient take a cold bath each morning. A cold bath for fifteen to thirty seconds frequently repeated may suffice to give tolerance. Cold sensitive patients are frequently hyperesthetic to cold. In this case, they may be unable to tolerate adequate exposure to cold during the early part of their treatment. After a time, they are likely to learn to enjoy exposure to cold. Frequently, patients tolerate a rapid rub with ice better than a cold bath. If the ice is moved rapidly enough over the skin, it does not cause a disagreeable sensation of cold. Ice

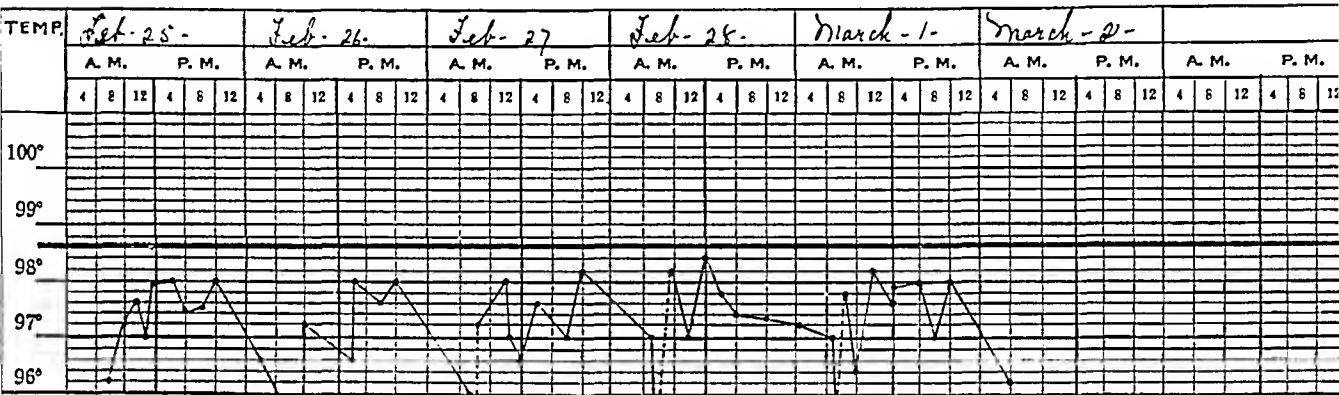


Fig. 9.—The temperature curve in a case of asthma caused by cold sensitiveness. The rises shown by the dotted lines were caused by a little exercise or by the application of heat in the form of a hot bath. If the temperature was raised each morning in this way, the patient remained comfortable throughout the day. If the temperature was not elevated in this way, he was subject to asthma which appeared on his being cooled or after prolonged quiet on his part. These attacks could be relieved immediately through exercise or the external application of heat, if these measures were used soon enough. This patient kept himself constantly comfortable through exercise, a hot bath and a cool shower taken soon after arising.

should be applied over the entire body and the rub should be completed, if possible, within less than one-half minute.

Symptomatic remedies suggested in the treatment of heat sensitive persons can be used to advantage in the treatment of cold sensitive patients. Also, if body temperature is inclined to be subnormal, the patient can frequently be benefited through the use of agents that raise temperature.

SUMMARY

In this paper are enumerated a series of relatively common illnesses which rather frequently are caused, I believe, by disorder in the heat



Fig. 10.—Case of summer dermatitis of face and neck of many years' duration caused by sensitiveness to heat. This eruption could be reproduced within a few minutes during the well period in the winter by immersing the arms in a water bath at 42 C. for less than five minutes, even though tourniquets were applied around the arms above the elbow so tight as to prevent a return of blood flow to the body. The itching, edema, and redness of the skin of the face caused in this way would disappear within a few moments if ice were applied to the fore-arms before removal of the tourniquets. The patient was relieved of summer dermatitis by spending the summer in an atmosphere which was cool and dry.

regulating mechanism. These illnesses included heat prostration, the effort syndrome, noninfectious coryza, asthma, urticaria, dermatoses and other miscellaneous ailments.

The heat regulating mechanism is important and extremely complex and for effectiveness requires the coordinated action of many structures that control heat production and heat loss. Of structures that seem important may be mentioned sense organs and cerebral centers that have a thermostatic effect on heat control; several hormones that effect both heat production and heat loss; histamine-like bodies that effect vascular tone; three important cooling surfaces, namely, the mucous membrane of the nose, the bronchial membrane and the skin; structures that control the secretion of moisture on cooling surfaces, and structures that control the depth and rapidity of respiration and the rate of blood flow to surfaces and to active internal organs.

I believe that under certain conditions this complicated mechanism is disordered at some point, and when disordered gives abnormal responses to sensations of heat and cold. Responses to heat and cold may then be inadequate to maintain ideal temperature, or exaggerated or in some cases perverted. Abnormal responses to change of temperature give rise more often, I believe, to pathologic changes than does any direct effect of a change in temperature on the tissues themselves.

Allergic reactions to foreign substances may give rise to symptoms similar to those of sensitiveness to heat or cold and may therefore add to the manifestations of heat and cold sensitiveness or in some instances may cause sensitiveness of this type for the time being.

In many persons, adequate cause for heat and cold sensitiveness can be discovered. In others, no pathologic process can be found, except abnormal responses to heat or cold. In this case, one frequently finds a history of an acute febrile disease just antedating the onset of the illness. It is generally stated in textbooks, and I believe correctly so, that in febrile diseases the heat regulating mechanism works at an abnormally high level so that responses to normal body temperature simulate those normally caused by reduction of heat. This gives rise to a retention of heat and a rise in temperature. In many instances, convalescence from an acute febrile disease is associated with a subnormal temperature for a varying period of time. I think that one can assume likewise, therefore, that during the period of convalescence from a febrile disease, the heat regulating mechanism is frequently working at an abnormally low level, so that a response to normal body temperature might simulate that normally caused by increased temperature and give rise to an unusually great loss of heat with a resulting fall in temperature.

It seems possible that under certain conditions the abnormal level at which the heat regulating mechanism works during a febrile disease

or during convalescence is maintained and gives rise to abnormal responses to heat and cold for prolonged periods of time or permanently. In many patients so afflicted, symptoms caused by heat and effort are identical while in others, symptoms caused by cold and inactivity are identical. In patients such as these, the ailments of which they complain can usually be reproduced objectively by the adequate and suitable application of heat and effort or by cold and inactivity.

During reactions of the types described caused by heat and cold sensitiveness, many patients are hypersusceptible to infection. It is believed that this type of sensitiveness plays a part in the susceptibility of many patients to the spring and fall epidemics, and finally in the complicating infections that often follow febrile diseases and in the predisposition of elderly people to respiratory infections.

The diagnosis of the condition can be made by history and practical tests.

The treatment of the condition is described in the text. It may be brilliantly successful in certain types of cases.

AREA OF THE BODY SURFACE AND MEASUREMENTS OF THE NORMAL HEART IN CHILDREN

II. ROENTGEN STUDY *

R. W. KISSANE, M.D.

COLUMBUS, OHIO

In the preliminary report,¹ the necessity of finding a variable that has a close correlation with the size of the heart was emphasized, and the area of the body surface was suggested, because it includes other variables, such as height, weight, age, sex and diameter of the chest, when persons of ideal weight are used as a standard.

Smith and Bloedorn² used the area of body surface as a variable to determine the size of the heart, because the former is an index of the mass of actively functioning tissue. They expressed disappointment at the observations, because the individual measurements were scattered over a wide range, which was probably due to the presence of a number of persons in their series whose weights were above ideal; but even then, the range was less than it was when weight was used as a variable.

To determine the size of the heart for an area of body surface of less than 1.5 square meters, 100 children, between the ages of 3 and 14 years, with normal hearts and electrocardiograms, were measured.

METHOD

The height and weight without clothing was obtained in each case. Roentgenograms were made at a distance of 6 feet and measured for the transverse diameter of the heart and the diameter of the chest.

The cases were classified as to their relation to ideal weight for a given height and age, the table of Woodbury³ being used for subjects under 5 years of age, and the table of Baldwin and Wood⁴ for those above this age. For the determination of the area of body surface, the table of Benedict and Talbot⁵ gave the best results.

* Submitted for publication, June 10, 1929.

* From the Departments of Cardiology, White Cross Hospital and Children's Hospital.

1. Kissane, R. W.: Area of the Body Surface and Measurements of Normal Hearts, *Arch. Int. Med.* **42**:135 (July) 1928.

2. Smith, H. W., and Bloedorn, W. A.: The Size of the Normal Heart: A Teleroentgen Study, *U. S. Navy Med. Bull.* **16**:234 (Feb.) 1922.

3. Woodbury, R. M.: Children's Bureau, U. S. Department of Labor.

4. Baldwin, B. T., and Wood, T. D.: Unpublished, Continental Scale Works, Chicago.

5. Benedict and Talbot: Pub. 302, Carnegie Institution, Washington, 1921, p. 61.

Besides the actual area of body surface in each case, the ideal weights were also determined for those who were 10 per cent above the ideal weight. They were classified into groups with a class interval of 0.1 square meter (table 1), and the mean and range of each class interval were established; this was also done for the children of ideal weight and for those under ideal weight, and a comparison was then made (table 2).

TABLE 1.—*Cases Grouped According to Surface Area*

Number	Body Surface Area	Ideal Weight Surface Area	Height, Cm.	Weight, Kg.	Ideal Weight, Kg.	Age, Years	Sex†	Chest Diameter, Cm.	Heart Transverse Diameter, Cm.
1	0.566	0.657	96.5	12.7	15	3	♀	15.4	7
2	0.566	0.657	96.5	12.2	15	3	♀	15.8	7.7
3	0.597	0.686	104.1	13.6	16.3	3	♀	16	7.8
4	0.597	0.872	119.3	13.6	22.2	6	♀	18.9	8.9
5	0.627	124.3	14.5	8	♀	18.8	9.2
6	0.686	0.796	115.5	16.8	20.4	8	♀	17.8	8
7	0.657	0.769	111.5	15.4	19	5	♀	18.6	8.7
8	0.686	0.742	110.4	16.8	18.6	6	♀	17.5	7.5
9	0.627	0.714	105.4	14.5	17.7	4	♀	16.5	8.5
10	0.645	101.0	15.2	4	♂	17	8.5
11	0.616	100.3	14.7	3	♂	16.8	7.7
12	0.616	91.4	14.5	3	♂	15.8	8.2
13	0.657	0.999	127.7	15.6	27.7	9	♀	18.8	8.6
14	0.645	0.74	106.6	15	17.7	4	♀	16	8.2
15	0.686	0.769	111.5	16.3	19	6	♀	16.6	7.9
16	0.686	109.2	16.8	5	♀	17.6	8
17	0.686	110.4	16.3	4	♀	17.8	7.8
18	0.796	120.6	20.6	7	♀	17.5	6.2
19	0.769	0.879	116.8	18.6	22.7	6	♂	15	9.4
20	0.769	0.879	116.8	18.8	22.7	7	♂	18.6	9.7
21	0.769	113.3	19.3	6	♀	17.6	8.9
22	0.74	109.2	17.2	5	♂	18.8	8.5
23	0.769	104.1	18.1	5	♂	16.5	9.5
24*	0.797	100.3	19.5	4	♂	17.8	8.5
25	0.797	0.932	121.9	19.3	24	8	♂	18.6	8.7
26	0.74	106.6	17.7	4	♂	18.3	8.5
27	0.769	109.2	18.1	7	♂	17.4	8.8
28	0.714	104.1	17	6	♀	17.5	8.6
29	0.74	0.825	111.5	17.7	20	4	♂	18.4	8.6
30*	0.797	106.6	19.7	5	♂	18.3	8.1
31	0.742	111.3	18.6	6	♂	17.3	8.3
32	0.74	106.6	17.2	6	♂	18.3	7.8
33	0.769	106.6	18.1	5	♂	17.4	9.5
34	0.742	112.4	18.1	7	♂	15.5	7.6
35	0.796	118.1	20.4	8	♀	17.5	8.8
36	0.796	119.3	20.4	5	♂	16.5	8
37	0.769	111.5	18.1	5	♂	18	8.9
38	0.711	106.6	16.8	5	♂	18.4	9.2
39	0.872	125.7	22.9	9	♂	18.3	9.1
40	0.853	0.958	124.3	21.1	25	10	♂	19	9.6
41	0.872	124.3	22.7	6	♀	18.1	8.4
42	0.845	121.9	21.1	8	♀	19.2	9.2
43	0.872	121.9	22.7	7	♀	20.6	9.5
44	0.825	118.1	20.4	7	♀	19.3	9.1
45	0.853	116.8	21.8	6	♀	19.4	9.2
46	0.898	1.048	131.8	23.8	29	10	♀	20	7.9
47	0.872	1.035	130.8	22	27.7	7	♀	20.2	9.9
48	0.872	0.949	123.2	22.7	25.9	8	♀	17.5	8.5
49	0.845	119.3	21.3	6	♀	18.5	9.4
50	0.845	121.9	21.1	8	♀	21.6	9.2
51	0.879	1.009	123.2	22.5	26.3	11	♀	20.1	10.2
52	0.872	0.949	127	22	25.9	8	♂	20	8.9
53	0.879	1.009	128.2	22.9	26.3	7	♂	20.6	9
54	0.879	120.6	22.7	6	♂	21.4	10.8
55	0.853	1.009	127	21.8	26.3	8	♂	19	10.1
56	0.853	121.9	21.3	6	♂	18.7	9
57	0.825	120.6	20.4	8	♀	17.4	8.8
58	0.879	1.009	127.6	22.7	26.3	8	♀	19.7	8.7
59	0.974	125.7	26.1	8	♀	19.8	9.5
60	0.924	124.3	24	5	♀	19.6	8.9
61	0.949	124.3	25	7	♀	18.7	9.7
62	0.906	123.1	23.6	7	♂	18.6	8.6

TABLE 1.—Cases Grouped According to Surface Area—Continued

Number	Body Surface Area	Ideal Weight Surface Area	Height, Cm.	Weight, Kg.	Ideal Weight, Kg.	Age, Years	Sex†	Chest Diameter, Cm.	Heart Transverse Diameter, Cm.
63	0.974	1.142	140.9	26.1	33.6	11	♀	18.2	8.9
64	0.974	133.3	26.8	26.8	10	♀	18.9	9.7
65	0.924	1.024	131.8	24.3	23.6	7	♀	19.1	9.7
66	0.924	0.999	127.7	24	27.7	9	♀	18.6	9.8
67	0.949	1.048	134.6	25.9	30.9	10	♀	20.2	7.9
68	0.924	1.134	137.1	24	31.8	7	♀	19.2	7.9
69	0.949	1.164	142.2	25	34	8	♀	21	9.8
70	0.932	121.9	24	7	♀	19.4	10.3
71	0.974	127	26.8	6	♀	18.2	8.7
72	0.924	128.2	24.5	9	♀	19.3	9.4
73	0.958	127.7	25	7	♀	20	9.2
74	0.999	134.6	27.2	11	♀	19.4	10.3
75	0.958	1.11	134.6	25.2	30.4	10	♀	19	8.2
76	0.999	1.164	139.7	27.2	34	12	♀	20.1	9.9
77	0.924	1.086	131.8	24.5	29	8	♀	20	9.7
78	1.048	138.4	29.5	9	♀	20.8	10.1
79	1.024	130.8	28.1	11	♀	20.1	9.5
80	1.024	130.8	28.4	8	♀	20.7	9.1
81	1.035	130.8	27.5	7	♀	18.9	8.3
82	1.06	1.134	137.1	28.1	31.8	10	♀	19.8	9.6
83	1.095	137.1	31.5	11	♀	22.4	10.8
84	1.086	1.202	142.2	29.5	34	8	♀	23.6	9.5
85	1.06	127.7	28.1	8	♀	23.4	9.4
86	1.06	1.4	154.9	28.4	43.6	12	♀	21.6	10.2
87	1.11	1.3	148.5	30.9	38.1	10	♀	19.5	8.7
88	1.159	1.254	144.7	32	36.8	12	♀	22.8	10.2
89	1.134	1.254	144.7	31.8	36.3	10	♀	21.6	9.4
90	1.188	142.2	35	11	♀	20.3	10.7
91	1.11	137.1	30.4	11	♀	22.3	10.5
92	1.142	140.9	33.6	10	♀	19.1	10.5
93	1.277	1.4	154.9	39.5	45	11	♀	24	10.2
94	1.254	1.4	154.9	36	45	14	♀	22.6	10
95	1.21	1.33	153	36.3	43.1	11	♀	20.7	9.3
96	1.21	1.33	152.4	36.8	43.1	11	♀	23.6	9.8
97	1.255	1.5	160	38	50.9	14	♀	22.1	8.9
98	1.207	152.3	34.5	11	♀	19.8	9.1
99	1.207	1.345	149.2	34.3	40.4	13	♀	22.4	10
100	1.44	160	45.6	14	♀	23.4	12.2

* Over ideal weight.

† In this column, ♂ stands for male; ♀, female.

TABLE 2.—Average and Range of Heart Measurements in Each Group

Surface Area Group Square Meters		Ideal* Weight, Kg.	Under Weight, Kg.	Entire Group, Kg.
From 0.5 to 0.59	Average.....	7.8	7.7
	Number.....	4	4
	Limits.....	7.0-8.9	7.0-8.9
0.6 to 0.69	Average.....	8.1	8.2	8.2
	Number.....	6	8	13
	Limits.....	7.5-9.2	7.8-8.7	7.5-9.2
0.7 to 0.79	Average.....	8.4	9.2	8.5
	Number.....	15	3	21
	Limits.....	6.2-9.2	8.7-9.7	6.2-9.7
0.8 to 0.89	Average.....	9.2	9.2	9.2
	Number.....	11	11	20
	Limits.....	8.4-10.8	7.9-10.2	7.9-10.8
0.9 to 0.99	Average.....	9.4	9	9.2
	Number.....	10	8	18
	Limits.....	8.6-10.3	7.9-9.9	7.9-10.3
1 to 1.09	Average.....	9.5	9.7	9.6
	Number.....	6	4	10
	Limits.....	8.3-10.8	9.5-10.2	8.3-10.8
1 to 1.19	Average.....	10.5	9.4	10
	Number.....	3	3	6
	Limits.....	10.5-10.7	8.7-10.2	8.7-10.7
1 to 1.29	Average.....	9.6	9.6	9.6
	Number.....	2	5	7
	Limits.....	9.1-10.2	8.9-10	8.9-10.2
1 to 1.39	Average.....
	Number.....
	Limits.....
1 to 1.49	Average.....	12.2	12.2
	Number.....	1	1
	Limits.....	12.2	12.2

* Only three cases in this group; therefore these averages were not used.

The cases of under ideal weight were subdivided into subgroups according to what the area of body surface would have been if the weight had been ideal (table 3). These figures were compared with the mean and range in the various class intervals of the ideal weight group, the entire group and one another.

TABLE 3.—*Groups the Children Would Be Classified in if of Ideal Weight for Height and Age*

Groups, Sq. Meters		0.6 to 0.699	0.7 to 0.799	0.8 to 0.899	0.9 to 0.999	1 to 1.09	1.1 to 1.19	1.2 to 1.29	1.3 to 1.39	1.4 to 1.49	1.5 to 1.59
0.5 to 0.599	Average, cm.....	7.5	...	8.9
	Number.....	3	...	1
	Range, cm.....	7-7.8	...	8.9
0.6 to 0.699	Average, cm.....	...	8.1	...	8.6
	Number.....	...	6	...	1
	Range, cm.....	...	7.8-8.7	...	8.6
0.7 to 0.799	Average, cm.....	9	8.7
	Number.....	3	1
	Range, cm.....	8.6-9.7	8.7
0.8 to 0.899	Average, cm.....	9	9.3
	Number.....	3	6
	Range, cm.....	8.5-9.6	7.9-10.2
0.9 to 0.999	Average, cm.....	9.8	9.1	8.9
	Number.....	1	3	5
	Range, cm.....	9.8	7.9-9.7	7.9-9.9
1.0 to 1.09	Average, cm.....	9.6	9.5	...	10.2
	Number.....	1	1	...	1
	Range, cm.....	9.6	9.5	...	10.2
1.1 to 1.19	Average, cm.....	9.8	8.7
	Number.....	2	1
	Range, cm.....	9.4-10.2	8.7
1.2 to 1.29	Average, cm.....	9.7	10.1	8.9	...
	Number.....	3	2	1	...
	Range, cm.....	9.5-10	10-10.2	8.9	...

TABLE 4.—*Relationship of Transverse Diameter of the Heart to Weight*

Number of Cases	Weight, Kg.	Average Transverse Diameter, Cm.	Number of Cases	Weight, Kg.	Average Transverse Diameter, Cm.
2.....	12	7.3	3.....	27	9.5
2.....	13	8.3	6.....	28	9.5
4.....	14	8.4	2.....	29	9.8
4.....	15	8.5	2.....	30	9.6
6.....	16	8	2.....	31	10.1
5.....	17	8.4	1.....	32	10.2
8.....	18	8.9	1.....	33	10.5
4.....	19	8.2	2.....	34	9.5
5.....	20	8.7	1.....	35	10.7
7.....	21	9.5	1.....	36	9.7
10.....	22	9.3	37	...
2.....	23	8.2	1.....	38	8.9
6.....	24	9.3	1.....	39	10.2
5.....	25	8.9	1.....	45	12.2
4.....	26	9.2			

Age, sex (table 9), weight (table 4), height (table 5) and the diameter of the chest (table 6) being used as variables, the mean transverse diameter of the heart for each class interval was determined and compared with the curves in this study, the area of body surface being used as a variable, and with the curves of other investi-

gators, Lincoln and Spillman's ⁶ age and sex curves, and Ziskin's ⁷ age and height curves (tables 7 and 8).

In order to find the mean transverse diameter of the heart and the range for each class interval of the body surface area from 0.5 to 2.1

TABLE 5.—*Relationship of Transverse Diameter of the Heart to Height*

Number of Cases	Height, Inches	Average Transverse Diameter, Cm.	Number of Cases	Height, Inches	Average Transverse Diameter, Cm.
1.....	36	8.2	8.....	50	9.1
.....	37	...	8.....	51	9.2
2.....	38	7.3	4.....	52	9.2
2.....	39	8.1	3.....	53	8.8
1.....	40	8.5	5.....	54	9.7
3.....	41	8.6	3.....	55	9.7
7.....	42	8.5	3.....	56	10
5.....	43	8.1	2.....	57	9.8
6.....	44	8.4	3.....	58	9.2
2.....	45	8.1	59	...
5.....	46	8.2	2.....	60	9.5
6.....	47	9.1	3.....	61	10.1
7.....	48	9.2	62
7.....	49	9	2.....	63	10.5

TABLE 6.—*Relationship of Transverse Diameter of the Heart to the Chest Diameter.*

Number of Cases	Chest Diameter, Cm.	Average Heart Transverse Diameter, Cm.
4.....	15-15.9	7.6
7.....	16-16.9	8.2
15.....	17-17.9	8.4
23.....	18-18.9	8.8
18.....	19-19.9	9.3
15.....	20-20.9	9.5
5.....	21-21.9	9.8
6.....	22-22.9	10
4.....	23-23.9	10.2
1.....	24-24.9	10.2

TABLE 7.—*Ziskin's Age Curves*

Age	Number of Cases	Transverse Diameter, Cm.
4.....	12	8.71
5.....	17	8.51
6.....	39	8.64
7.....	20	9.05
8.....	80	8.91
9.....	49	9.25
10.....	48	9.38
11.....	57	9.59
12.....	20	9.85
13.....	28	9.88
14.....	24	10.38
15.....	26	10.24
16.....	10	10.4

6. Lincoln, E. M., and Spillman, R.: Studies on the Hearts of Normal Children, Am. J. Dis. Child. **35**:791 (May) 1928.

7. Ziskin, Thomas: Development of Size of the Heart in Children, as Revealed by Teleroentgen-Ray Measurements, Am. J. Dis. Child. **30**:851 (Dec.) 1925.

square meters, this group of 100 children was added to the group of 438 men reported by Cohn⁸ and Smith⁹ and used in the preliminary report.¹ The following groupings were made and compared: the entire group, the entire male group, the males of ideal weight and the female group. A comparison was now made between the boys and girls with the area of body surface as a variable.

COMMENT

If the one case in the class interval from 1.4 to 1.49 square meters is disregarded, and the mean transverse diameter of the hearts in the

TABLE 8.—Ziskin's Height Curves

Height, Inches	Number of Cases	Transverse Diameter, Cm.
From 38 to 41.....	14	8.37
41 to 44.....	35	8.52
44 to 47.....	56	8.53
47 to 50.....	77	9.1
50 to 53.....	80	9.33
53 to 56.....	59	9.53
56 to 59.....	43	9.7
59 to 62.....	30	10
62 to 65.....	17	10.5
65 to 68.....	14	10.7

TABLE 9.—Relation of Transverse Diameter of the Heart to Age and Sex

Boys		Age, Years	Girls	
Number of Cases	Average Transverse Diameter, Cm.		Number of Cases	Average Transverse Diameter, Cm.
2	7.9	3	3	7.5
5	8.4	4	2	8.1
6	8.9	5	4	8.4
5	9.2	6	9	8.5
10	9	7	5	9
6	9.3	8	11	9
..	...	9	5	9.4
5	9.1	10	4	9
3	9.0	11	8	9.9
2	10.2	12	1	9.9
1	10	13
2	11.1	14	1	8.9

entire, under ideal and the ideal weight groups, with the area of body surface as a variable, is compared (table 2), the curve of the entire and the ideal weight groups is found to be the smoother, thereby showing good correlation, while the under ideal weight curve is more irregular. When the 438 adult males are combined with these cases and studied with regard to ideal weight, it is apparent that those in the ideal weight group have a smoother curve and better correlation than those in the entire group, the male group or the female group.

8. Cohn, A. E.: An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. **25**:499 (May) 1920.

9. Smith, B.: Teleroentgen Measurements of the Hearts of Normal Soldiers. Arch. Int. Med. **25**:522 (May) 1920.

Since the range in the entire group of children is the largest (table 2), and the ranges in the ideal and under ideal groups are practically the same, increase in weight causes an increase in range as it does in adults.

A curve of the mean transverse diameter of the hearts, with height as a variable, and a class interval of 1 inch, is irregular (table 5), which shows poor correlation, especially as compared with Ziskin's⁷ height curve for children (table 8); but this is due to the use of a larger class interval, 4 inches, which tends to make a smooth curve.

The curve with weight as a variable and a class interval of 1 Kg. is also irregular (table 4), which shows poor correlation. When the children are grouped according to sex and age is used as a variable (table 9), the curve shows a fair correlation of the mean transverse diameter of the heart, but not as good as that reported by Ziskin,⁷ and the size of the heart of the girls is smaller than that of the boys at any given age, thereby disagreeing with the observations of Lincoln and Spillman⁸ that until the age of 7 the hearts of girls are smaller than those of boys, but that after 11 years of age, this condition is reversed.

A curve of the mean transverse diameter of the heart with the diameter of the chest as a variable and a class interval of 1 cm. shows good correlation (table 6). The area of body surface and the diameter of the chest have a closer correlation to the size of the heart in children than age, height, weight or sex, and age has a closer correlation than height or weight; but since the area of body surface incorporates these other variables, and has the same relation to the size of the heart in children and adults, it is a clinical criterion for the estimation of the size of the normal heart with the best general correlation.

CONCLUSIONS

Cases of ideal weight for height should be used in the estimation of the measurements of normal hearts.

Cases of over or under ideal weight for height have an antagonistic influence on the close correlation of the area of body surface with the mean transverse diameter of the heart.

Increase in the weight of children as a group increases the range from the mean transverse diameter of the heart, with the area of body surface as a variable.

In this series of children, the mean transverse diameter of the hearts in girls was smaller than that in boys at any age. The area of body surface has the same close correlation to the size of the heart in children as in adults.

THE MECHANISM OF SECONDARY ANEMIA*

A. H. DOUGLAS, M.D.

AND

H. TANNENBAUM, M.D.

NEW YORK

Three mechanisms may be concerned in the production of anemia: (1) hemorrhage, (2) diminished production of blood or impaired delivery of erythrocytes from the hematopoietic tissue into the circulation and (3) destruction of blood. One might add hydremia, as, judged by the ordinary methods of clinical investigation, it would appear to be anemia.

In order to decide which of the aforementioned factors is active in the production of the common forms of secondary anemia, we attempted to determine whether in those conditions there is an abnormality in the formation or destruction of red blood cells. In this investigation we relied on the fact that the reticulated cell count furnishes the most accurate index of bone-marrow function available, and that the icteric index is a simple and reliable measure of breakdown of hemoglobin, except in patients with hepatic lesions or obstructed biliary passages.

Much work has been done recently both with the reticulated cell count and with the icteric index. The bulk of this work, however, has dealt with one or the other of these values separately. The only reference encountered in the literature involving both determinations is that of Dyke and Greener.¹ These authors reported the values in two cases of pernicious anemia, and demonstrated an increase in reticulocytes and a decreased icteric index during remissions of the disease. It is only with a knowledge of both values that one can classify the forms of anemia accurately and determine the cause in a given case. In table 1 appears the general scheme for such an analysis.

That the reticulocyte count is a reliable measure of the production of red blood cells is fairly well established. Hawes² showed that the count is high in childhood (up to 5.7 per cent) and following hemorrhage. Dameshek³ reported that the count surpasses 6 per cent before clinical evidence of a remission appears in pernicious anemia, and that

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* From the Department of Medicine, Cornell University Medical College, and the Second Medical (Cornell) Division, Bellevue Hospital.

1. Dyke, S. C., and Greener, J.: Reticulocyte Crises and Serum Bilirubin in Pernicious Anemia, *Lancet* **1**:1068, 1928.

2. Hawes, J. B.: A Study of the Reticulated Blood Corpuscles by Means of Vital Staining Methods, *Boston M. & S. J.* **161**:493, 1909.

3. Dameshek, W.: Reticulated Cells: Their Clinical Significance, *Boston M. & S. J.* **194**:759, 1926.

death follows repeated low counts. These observations strongly suggest that the appearance of reticulated cells in the circulation is associated with an active erythropoietic function.

As the reticulocyte count is a measure of erythrocyte formation, so is the icteric index a guide to the destruction of red blood cells, or, more exactly, to the breakdown of hemoglobin. The quantity of pigment indicated by the icteric index may include: (1) pigment derived from broken-down hemoglobin; (2) bilirubin further altered by liver cells and excreted into, but reabsorbed from, biliary channels; (3) bilirubin and hydrobilirubin absorbed from the intestine, and (4) food pigments, such as carotin and xanthophyll. The icteric index, of course, is a measure of blood destruction only when there is no injury

TABLE 1.—*The Relation of the Reticulated Cell Count to the Icteric Index*

Reticulated Cell Count	Normal or Low Icteric Index	High Icteric Index
High	Hemorrhage with good bone-marrow response	Destruction of blood with good bone-marrow response
Normal	Hemorrhage with poor regeneration by bone-marrow	Destruction of blood without good bone-marrow response
	Diminished* production of blood or impaired delivery of erythrocytes into the circulating blood	Destruction of blood without good bone-marrow response
Low	Hemorrhage with poor regeneration by bone-marrow	Destruction of blood or hemolytic anemia, with poor regeneration of red blood cells
	Diminished* production of blood during the transition from a higher to a lower number of red cells	Destruction of blood or hemolytic anemia, with poor regeneration of red blood cells
	Hydremia	

* When the output of new red blood cells is diminished, there is a decrease in the number of the younger reticulated cells before there is a corresponding reduction of adult erythrocytes. Hence, during the transition from 5,000,000 red blood cells per cubic millimeter to a lower figure, the ratio of reticulated cells to total erythrocytes is below normal. When a new equilibrium is established at the lower figure, the ratio returns to normal, although the total number of both reticulated and adult cells is low.

to the liver or biliary obstruction. To avoid the presence of food pigments and clouding of the serum by fat, one can draw blood for the determination at a suitable interval after meals, as Bernheim⁴ pointed out.

Some prefer the quantitative van den Bergh test to the icteric index. Bernheim, however, showed that the icteric index can be just as accurate and is to be preferred in cases of hypobilirubinemia; she advised that it be used as the simpler procedure.

The blood bilirubin in patients with anemia was studied first in cases of pernicious anemia. In 1917, Blankenhorn⁵ reported bile

4. Bernheim, A. R.: Significance of Variations of Bilirubinemia, Arch. Path. & Lab. Med. 1:747 (May) 1926.

5. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, Arch. Int. Med. 19:344 (March) 1917.

pigment in the blood in this type of anemia, and since then many writers have demonstrated hyperbilirubinemia in this disease—Perkins,⁶ St. George and Brown,⁷ Andrews,⁸ Hirshfeld,⁹ Lepehne¹⁰ and others. Much less work has been done on secondary anemia.

NORMAL VALUES

Normal standards for both determinations discussed have been definitely established. Hawes gave the normal range of reticulated cells as from 0.3 to 1.4 per cent, with 0.85 per cent as the average in fifteen subjects. More recently, Davidson and McCrie¹¹ gave 0.5 per cent as the average figure, and Krumbhaar¹² stated that from 0.2 per cent to 0.8 per cent covers the great majority of normal persons. The differences in the foregoing figures were probably due to variations in technic, but one may safely take 1.5 per cent as an upper limit and consider higher values as probably abnormal. According to Hawes' limits and the average normal total of 5,000,000 red blood cells per cubic millimeter, the normal total of reticulocytes may be given as from 15,000 to 70,000, with a mean of 43,000.

The normal icteric index varies, according to Stetten's¹³ determinations in 144 cases, from 2.5 to 5. St. George and Brown found that in 90.8 per cent of 120 normal subjects the rate fell between 3.5 and 5.5. They quoted similar figures obtained by van den Bergh, Hymans and Snapper.¹⁴ Bernheim's normal limits are from 4 to 6.

The values for serum bilirubin, expressed in milligrams per hundred cubic centimeters, that are given by Schiff,¹⁵ van den Bergh, Hymans

6. Perkin, F. S.: Estimation and Clinical Significance of the Icteric Index, *Arch. Int. Med.* **40**:195 (Aug.) 1927.

7. St. George, A. V., and Brown, A. L.: Value of Icteric Index in Differentiating Anemia, *Arch. Int. Med.* **36**:847 (Dec.) 1925.

8. Andrews, C. H.: A Clinical Study of van den Bergh's Test in Jaundice, *Quart. J. Med.* **18**:19, 1924.

9. Hirschfeld, H.: Ueber die Rolle der Milz in dem Pathogenes der perniziösen Anämie, *Ztschr. f. Klin. Med.* **87**:165, 1919.

10. Lepehne, G.: Weitere Untersuchungen über Gallenfarbstoff im Blutserum der Menschen, *Deutsches Arch. f. klin. Med.* **135**:79, 1921.

11. Davidson, L. S. P., and McCrie, J. G.: Phenomenon of Reticulation and Alteration in Size of Red Blood Corpuscles After Liver Therapy, *Lancet* **2**:1014, 1928.

12. Krumbhaar, E. B.: Increased Percentage of Reticulated Erythrocytes in the Peripheral Blood, *J. Lab. & Clin. Med.* **8**:11, 1922.

13. Stetten, De W.: Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, *Ann. Surg.* **76**:191, 1922.

14. Van den Bergh, A. A.; Hymans and Snapper: Die Farbstoffe des Blutserums, *Deutsches Arch. f. klin. Med.* **110**:540, 1913.

15. Schiff, L.: Serum Bilirubin in Health and Disease, *Arch. Int. Med.* **40**:800 (Dec.) 1927.

and Snapper, Lepehne,¹⁶ McNee,¹⁷ Botzian,¹⁸ Wiemer¹⁹ and others, indicate that 1 mg. is a safe upper limit. This is roughly equivalent to an icteric index of 10,²⁰ or is somewhat higher than the upper limit of normal given.

METHODS

To investigate the mechanism of secondary anemia, the reticulocyte count and the icteric index of thirty-four patients in the wards of the second medical division of Bellevue Hospital were determined.

The reticulated cell counts were made with the technic described by Hawes and Cunningham,²¹ except for a slight modification. This consisted in leaving the blood in contact with the brilliant cresyl blue for from twenty to thirty minutes, instead of the thirty seconds recommended, so as to give more time for the diffusion of the dye and for staining. As evaporation can occur only at the edges of the coverslip, it never was sufficient to cause crenation of the corpuscles in this time. When the counts were being made, the number of reticulated cells was noted while one thousand red blood cells were counted.

Total red blood cell counts were made with the use of standardized pipets and an improved Neubauer chamber. The same chamber was used for all the counts. The hemoglobin percentage was determined with a Dare hemoglobinometer, which had been matched against a Sahli instrument provided with a glass standard. The blood for the three determinations mentioned was drawn from the finger with a single puncture.

The blood for the icteric index was drawn from the median cubital vein within one hour after obtaining the blood for the other determinations; 10 cc. was drawn with a syringe which had been previously rinsed with physiologic solution of sodium chloride to avoid hemolysis. The blood was collected in large cotton-plugged test tubes which were then placed in the icebox. The supernatant serum was used for the determination. The serum was allowed to clear by standing; centrifugating was resorted to only when it was suspected that suspended corpuscles were present, or when the serum was turbid.

Readings were made by daylight with a Duboscq colorimeter in which undiluted serum was compared with the standard set at the 15 mark. Readings were all made within twenty-four hours after the blood was drawn. The standard used was a 0.01 per cent aqueous solution of potassium dichromate to which 4 drops of concentrated sulphuric acid per thousand cubic centimeters had been added to prevent fading.

In this study the intervals of time between meals and the drawing of blood could not be observed, but apparently this did not affect the results obtained.

16. Lepehne, G.: Untersuchungen über Gallenfarbstoff im Blutserum d. Menschen, *Deutsches Arch. f. klin. Med.* **132**:96, 1920.

17. McNee, J. W.: Use of the van den Bergh Test in the Differentiation of Obstructive from Other Types of Jaundice, *Brit. M. J.* **1**:716, 1922; Jaundice: A Review of Recent Work, *Quart. J. Med.* **16**:390, 1923.

18. Botzian, R.: Beiträge zur Bilirubingehalt des menschlichen Serums bei Gesunden und Kranken, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **32**:549, 1920.

19. Weimer, P.: Ueber d. Direkte und Indirekte Diazo-Reaktion in Blutserum, *Deutsches Arch. f. klin. Med.* **151**:154, 1926.

20. Cullen, C.; Emerson, E. E., and Woodruff, W.: Icteric Index, Spectrophotometric and Quantitative Studies, *Arch. Int. Med.* **41**:428 (March) 1928.

21. Cunningham, T. D.: A Method for Permanent Staining of Reticulated Red Cells, *Arch. Int. Med.* **26**:405 (Oct.) 1920.

RESULTS

The cases studied may be grouped as follows: (1) secondary anemia with no evidence of hemorrhage or obvious destruction of blood, (2) secondary anemia with hemorrhage and (3) nonanemic subjects, including normal controls.

Twenty-five patients with secondary anemia, none of whom presented evidence of hemorrhage or of conditions known to destroy blood, had normal reticulocyte counts, varying from 0.1 to 1.4 per cent (with the exception of two patients showing 2 per cent), (table 2). The average was 0.85 per cent and the majority were between 0.8 and 1.1 per cent. These figures coincide with the values in normal subjects given by Hawes. The totals varied from 3,000 to 74,000 per cubic millimeter, with an average of 34,000 and a median of from 40,000 to 50,000. The icteric indexes ranged from 2.6 to 15. Elimination of the high indexes in cases of cardiac insufficiency with possible hepatic congestion, gives 2.6 and 8.2 as the limits for twenty cases, with a normal average of 5.3.

In six patients with anemia due to hemorrhage, shown in table 3, the reticulocyte count was normal or high, varying from 1 to 5 per cent. The average, 1.9 per cent, was above the upper limit of normal. The total counts lay within limits of from 20,000 to 130,000 per cubic millimeter, with an average of 61,000. The icteric indexes were normal or low in the uncomplicated cases (from 2.6 to 8). In one case (case 3) giving a high figure there was evidence of injury to the liver, and in the other (case 6) the patient died a few hours after blood was drawn. In case 3 (table 3) the rise in the reticulated cell ratio and total can be followed in repeated counts as the total number of red blood cells increased.

Table 4 includes seven nonanemic subjects. The reticulated cell counts, varying from 0.3 to 1.3 per cent, lie within the normal limits. The icteric indexes range from 4 to 9.6 and include some values slightly above the normal limits set by Bernheim.

COMMENT

In this study, most of the cases fall into the group of secondary anemia without hemorrhage or known hemolytic disease. Very few reticulocyte counts in such cases are available in the literature. The values found here, and recorded in table 2, are within the normal limits obtained by Hawes. They are somewhat above normal if Krumbhaar's figures are accepted. It may be that in this work the longer contact between cells and vital stain increased the number in which the reticulum was made visible. The total number of reticulocytes per cubic milli-

TABLE 2.—*Reticulated Cell Count and Icteric Index in Secondary Anemia with no Evidence of Hemorrhage*

Patient	Sex	Age	Diagnosis	Hemo- globin	Number Red Blood Cells per C.Mm.	Number Reticulo- cytes per 1,000 Red Blood Cells	Number Reticulo- cytes per C.Mm. Blood	Icteric Index	Remarks
1	M	..	Syphilitic aortitis, subacute bacterial endocarditis	41	3,980,000	9 (0.9%)	36,000	5.0	
2	M	25	Tonsillitis, arthritis, myositis	65	4,500,000	5 (0.5%)	22,500	5.6	
3	M	..	Grip, infectious arthritis	53	3,670,000	9 (0.9%)	33,000	5.0	
4	M	48	Infectious arthritis, auricular fibrillation	58	3,700,000	14 (1.4%)	52,000	4.6	
5	M	30	Gonococcal arthritis	55	4,350,000	8 (0.8%)	25,000	5.7	
6	M	52	Syphilis, lead pois- oning (?)	65	3,500,000	11 (1.1%)	38,500	4.1	
7	M	60	Syphilitic aortitis, decompensation	68	4,380,000	10 (1.0%)	44,000	6.0	
8	M	46	Chronic interstitial nephritis	57	3,520,000	14 (1.4%)	50,000	4.6	Thirteen days before, hemo- globin was 43 and red blood cells 3,510,000
9	M	42	Chronic nephritis, hypertension, cardiac failure	72	3,770,000	3 (0.3%)	11,000	12.0	
10	F	40	Chronic interstitial nephritis	44	2,500,000	3 (0.3%)	7,500	8.2	
11	F	23	Pericarditis	76	5,300,000	11 (1.1%)	58,000	5.3	
12	M	16	Acute rheumatic fever, carditis	55	4,100,000	3 (0.3%)	12,000	4.7	
13	M	23	Rheumatic disease of the heart, poly- arthritis	69	4,500,000	4 (0.4%)	18,000	7.0	
14	F	16	Chorea	48	5,400,000	4 (0.4%)	22,000	5.0	
15	M	18	Rheumatic disease of the heart, auricular fibrillation decompensation	65	5,300,000	8 (0.8%)	42,000	14.0	Nine days previ- ously, hemo- globin was 60 and red blood cells 5,170,000
16	Acute rheumatic fever, endocarditis, fibrinous pleurisy	45	3,270,000	1 (0.1%)	3,000	4.9	
17	F	34	Abscess of the lung (post-pneumonic)	60	3,100,000	10 (1.0%)	31,000	5.8	Ten days previ- ously, hemo- globin was 50
18	M	..	Abscess of the lung	76	4,710,000	10 (1.0%)	47,000	7.8	
19	M	45	Abscess of the lung	36	2,860,000	20 (2.0%)	57,000	5.5	Two days later, red blood cells were 3,000,000 and hemo- globin 40
20	F	23	Chronic pulmonary tuberculosis	64	4,750,000	6 (0.6%)	28,500	5.0	
21	F	44	Lobar pneumonia	34	3,800,000	5 (0.5%)	19,000	3.0	
22	F	27	Chronic cardiovas- cular disease	80	4,900,000	2 (0.2%)	10,000	11.0	
23	F	45	Chronic myocarditis, general arterio- sclerosis, brachial and facial neuralgia	70	4,700,000	10 (1.0%)	47,000	8.8	
24	M	38	Echinococcus (liver), chronic bronchitis, fibrinous pleurisy, myocarditis	60	3,700,000	20 (2.0%)	74,000	2.6	
25	F	65	Chronic nephritis, general arterio- sclerosis, auricular fibrillation, decompensation	55	3,950,000	12 (1.2%)	47,000	1.5	
Average						8.5	34,000	6.6	
Median						8-11	40-50,000		
Excluding cases with cardiac insufficiency, average.....								5.3	

meter would be more significant, as Johnson and Berglund²² pointed out, if the trend were known in each case, i. e., whether the number of red blood cells was increasing or decreasing at the time of the count.

TABLE 3.—*Reticulated Cell Count and Icteric Index in Secondary Anemia with Evidence of Hemorrhage*

Patient	Sex	Age	Diagnosis	Hemo-globin	Number Red Blood Cells per O.Mm.	Number Reticulo-cytes per 1,000 Red Blood Cells	Number Reticulo-cytes per O.Mm. Blood	Icteric Index	Remarks
1	M	52	Gastro-Intestinal bleeding	29	2,000,000	10 (1.0%)	20,000	2.6	
				35	2,528,000	3.0	Twenty-one days previously
2	M	40	Carcinoma of rectum	40	3,635,000	16 (1.6%)	58,000	6.5	
3	F	25	Pulmonary tuberculosis, gastro-intestinal bleeding, cirrhosis	48	3,680,000	21 (2.1%)	77,000	16.55	Nov. 20, 1928
			alcoholic neuritis	38	1,060,000	Nov. 6, 1928; reaction to van den Bergh direct test slightly delayed; indirect slightly +
				54	2,320,000	12 (1.2%)	28,000	...	Nov. 9, 1928
				45	3,160,000	18 (1.8%)	57,000	...	Nov. 19, 1928
4	M	46	Bleeding duodenal ulcer	50	3,080,000	14 (1.4%)	43,000	8.0	
5	M	52	Chronic nephritis with edema and hypertension	50	2,700,000	14 (1.4%)	38,000	4.2	Intestinal hemorrhage four days before count
6	M	43	Hemorrhagic pericarditis	35	2,600,000	50 (5.0%)	130,000	10.0	Patient died on day of count
Average						19	61,000	7.9	
Excluding cases 3 and 6, average.....								5.3	

TABLE 4.—*Reticulated Cell Count and Icteric Index in Nonanemic Subjects*

Subject	Sex	Age	Diagnosis	Hemo-globin	Number Red Blood Cells per O.Mm.	Number Reticulo-cytes per 1,000 Red Blood Cells	Number Reticulo-cytes per O.Mm. Blood	Icteric Index
1	F	24	Normal	80	4,850,000	12 (1.2%)	58,000	9.6
2	M	24	Normal	85	5,900,000	4	21,000	7.5
3	M	23	Normal	90	5,420,000	13	70,000	9.6
4	M	23	Normal	75	4,800,000	8	38,000	7.7
5	F	..	Acute tonsillitis, erythema nodosum	84	4,900,000	12	58,000	4.0
6	M	52	Duodenal ulcer (healed).....	85	5,300,000	6	32,000	8.3
7	M	69	Chronic bronchitis, general arteriosclerosis	80	5,500,000	7	38,500	5.6
Average						8.8	46,000	7.5

In interpreting the icteric indexes, one must note the statement of St. George and Brown that, in their experience, cardiac insufficiency

22. Johnson, R., and Berglund, H.: Significance of the Reticulocyte as Index of Regeneration in Different Types of Experimental Anemia, Proc. Soc. Exper. Biol. & Med. **25**:517, 1928.

was one of the common disturbing factors which gave a high figure. Omitting such cases from our series, the results for secondary anemia, both with and without hemorrhage, are normal or low. This is in accord with the observations of other investigators. Bernheim²³ reported thirty-three cases of secondary anemia with hypobilirubinemia. St. George and Brown gave the following indexes: carcinoma with anemia, from 1.5 to 3; sarcoma, 1.8; lymphosarcoma, 2; Hodgkin's disease, 2; fibromyoma, 1; ulcerative colitis, 1.5, and gastric ulcer, 3. Perkins found from 1 to 3.5 mg. of bilirubin per thousand cubic centimeters of blood (from 1 to 3.5 icteric index units) in secondary anemia.

To summarize the results for group 1, it may be said that in secondary anemia without hemorrhage or conditions known to destroy blood, a normal reticulocyte count and a normal or low icteric index are found. The type of anemia in this group, therefore, cannot be due to destruction of blood. Hemorrhage having been excluded,

TABLE 5.—*Reticulated Cell Count and Icteric Index in All Subjects Studied*

Cases	Average Number Reticulocytes per 1,000 Red Blood Cells	Average Number Reticulocytes per C.Mm. of Blood	Average Icteric Index
25 cases; secondary anemia with no evidence of hemorrhage	8.5 (0.85%)	34,000	6.6
20 cases of the foregoing group, eliminating those with cardiac insufficiency	5.3
6 cases; secondary anemia with evidence of hemorrhage	21 (0.20%)	61,000	7.9
4 cases of foregoing group, eliminating those with hepatic damage	5.3
7 nonanemic subjects	8.8 (0.88%)	46,000	7.5

diminished production of blood must be regarded as causal, in spite of the normal reticulocyte count; as has been explained, when equilibrium at the anemic level is achieved, the ratio of reticulocytes to erythrocytes is normal. Hydremia as a factor is to be thought of chiefly in connection with the anemia of nephritis. However, if it were the sole factor in the type of case illustrated by patient 10 (table 2) the volume of blood would have to be doubled. In the anemia of chronic nephritis, however, there is no increase in volume of the blood, judging from the few cases studied by Brown and Roth,²⁴ Keith, Rowntree and Geraghty,²⁵ and Bock.²⁶ These authors did not include cases of chronic

23. Bernheim, A. R.: The Icterus Index (A Quantitative Estimation of Bilirubinemia, J. A. M. A. **82**:291 (Jan. 26) 1924.

24. Brown, G. E., and Roth, G. M.: Anemia of Chronic Nephritis, Arch. Int. Med. **30**:817 (Dec.) 1922.

25. Keith, N. M.; Rowntree, C. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.

26. Bock, A. V.: The Constancy of the Volume of the Blood Plasm, Arch. Int. Med. **27**:83, 1921.

nephritis with anemia and without edema. It is possible that in this condition, dilution of the blood is a factor, in spite of the leukocytosis found as a rule in these cases. Points in favor of hydremia are the relatively infrequent association of anemia and edema in cases of chronic nephritis (Brown and Roth), and the demonstration by MacLean²⁷ of a fall in blood pressure and rise of hemoglobin with increase in the volume of urine in cases of acute nephritis. Hydremia, therefore, cannot with certainty be ruled out as a possible factor in the anemia of nephritis, although it is probably not the chief cause of anemia in that condition.

The diminished production of blood in the type of anemia discussed may theoretically be due to toxic action on, or circulatory changes in, the hematopoietic system. Whatever the mechanism, hemoglobin synthesis is affected more than the production of red cells since the color index is low.

In the five patients suffering from secondary anemia with hemorrhage, the reticulocyte counts were normal or high. This agrees with the observations of others. Hawes' figures have been quoted. Davidson and McCrie stated that hemorrhage may raise the reticulocyte count to 35 per cent. Our highest figure was 5.8 per cent. In none of the cases was the count low.

In these cases the reticulocyte count varied from normal to high according to the response of the bone-marrow to the demands for increased function. As the cells were removed intact from the circulation, there was no reason to expect an increase in the icteric index.

Of the seven nonanemic subjects, two had icteric indexes which were somewhat high—9.6. In other respects, the observations agree with those of other investigators.

SUMMARY AND CONCLUSIONS

1. Cases of anemia may be grouped etiologically if the reticulocyte count and the icteric index are known. They may be classified as due to: (a) hemorrhage; (b) diminished production of blood, or faulty delivery of the red cells into the circulating blood; (c) destruction of blood or (d) combinations of these factors.

2. In twenty cases of secondary anemia without hemorrhage, the reticulocyte counts were normal and the icteric indexes normal or low.

3. The common form of secondary anemia found in such chronic conditions as nephritis or abscess of the lung and in some of the acute infections (particularly acute rheumatic fever) is the result of the diminished production of blood.

27. MacLean, H.: *Diagnosis and Treatment of Renal Diseases*, ed. 3, Philadelphia, Lea & Febiger, 1927, p. 19.

TWENTY-FOUR HOUR BLOOD SUGAR VARIATIONS IN FASTING AND IN NONFASTING SUBJECTS*

J. SHIRLEY SWEENEY, M.D.

DALLAS, TEXAS

As the response of the diabetic patients to food is the same as that of the normal person save for the varying degrees of deficiency of endogenous insulin, it was thought that the knowledge of normal fluctuations of the blood sugar over a period of twenty-four hours might prove of value in the management of diabetic cases. There have appeared in the literature studies of blood sugar variations in diabetic and in nondiabetic persons. From these studies suggestions have been offered to facilitate the handling of diabetes as regards the time insulin should be given, the dosage, etc. Jonas and his associates¹ studied all day blood sugar curves in diabetic and nondiabetic persons. They found from their observations that mild cases of diabetes may be controlled by a single morning dose of insulin, owing to the tendency of the blood sugar to be rising or to rise higher after this meal; that two doses are often necessary, in which cases the afternoon dose is usually smaller than the morning dose, and that the lowest blood sugar is usually noted just before the midday meal or in the afternoon. The present study was made for the purpose of confirming in part the aforementioned investigators' observations and to determine the blood sugar variations during fasting over a period of twenty-four hours.

Eight medical students free from organic ailments were used in this study. Four of the students were allowed "general diets" and four were deprived of all food for the twenty-four hours. Blood sugar determinations by the Folin-Wu method were made every two hours throughout the twenty-four hours on both groups. The readings were all made by me. The results of these observations are so uniform that additional observations were considered unnecessary.

In the accompanying table are listed the results in the fasting and nonfasting subjects. The same data are presented graphically in charts 1 and 2. In chart 3 may be seen the composite twenty-four hour curves of the two groups.

* Submitted for publication, June 20, 1929.

* From the Department of Internal Medicine, Baylor University.

1. Jonas, L.; Miller, T. G., and Teller, I. A.: All Day Blood Sugar Curves in Nondiabetic Individuals and in Diabetic Patients With and Without Insulin, *Arch. Int. Med.* **35**:289 (March) 1925.

COMMENT

There are several interesting suggestions to be noted. The first is that in the fasting group the twenty-four hour curve is practically flat. There is a very slight rise beginning in the early morning which con-

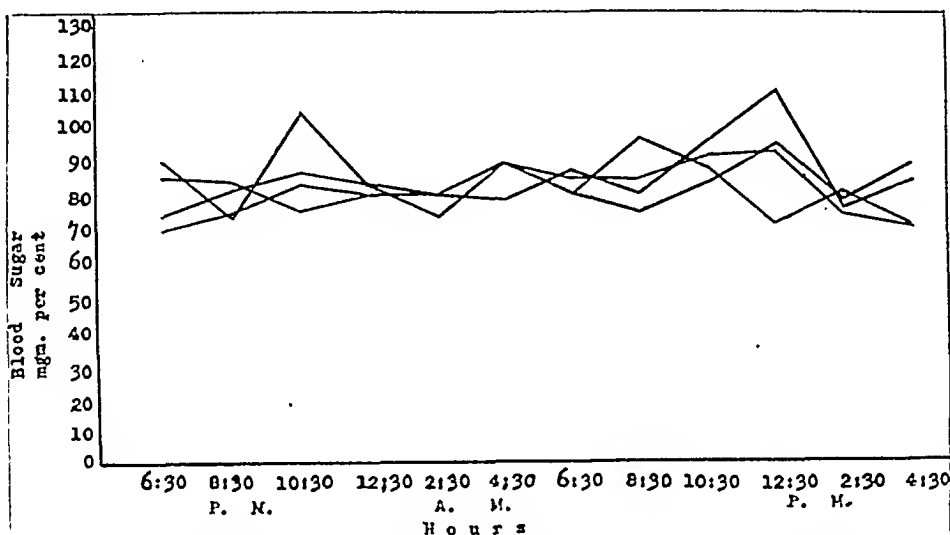


Chart 1.—Two-hourly variations of blood sugars over a period of twenty-four hours in fasting normal persons. (It will be noted in all the charts that the variations appear greater than they really are owing to a rather fine ordinate scale.)

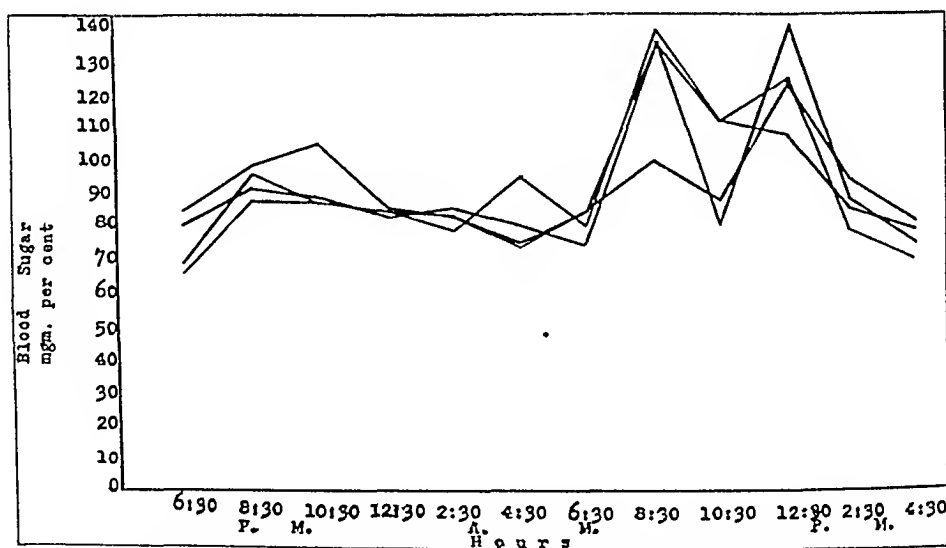


Chart 2.—Two-hourly variations of blood sugars over a period of twenty-four hours in nonfasting normal persons.

tinues to the noon hour and then drops. Although these changes are small, they suggest what may be termed a normal tendency, a conditioned vegetative response so to speak.

In the nonfasting group will be seen a rather insignificant rise following the evening meal, with a subsequent flat curve through the night hours. In the early morning hours, especially following breakfast, occurs a sharp and significant rise followed by a short decline. This is followed by a rise following the midday meal with a subsequent definite drop which is only slightly affected by the evening intake of food.

The explanation and practical significance of these changes are interesting. It has now been shown² and well established that food, especially carbohydrates, stimulates the production of endogenous

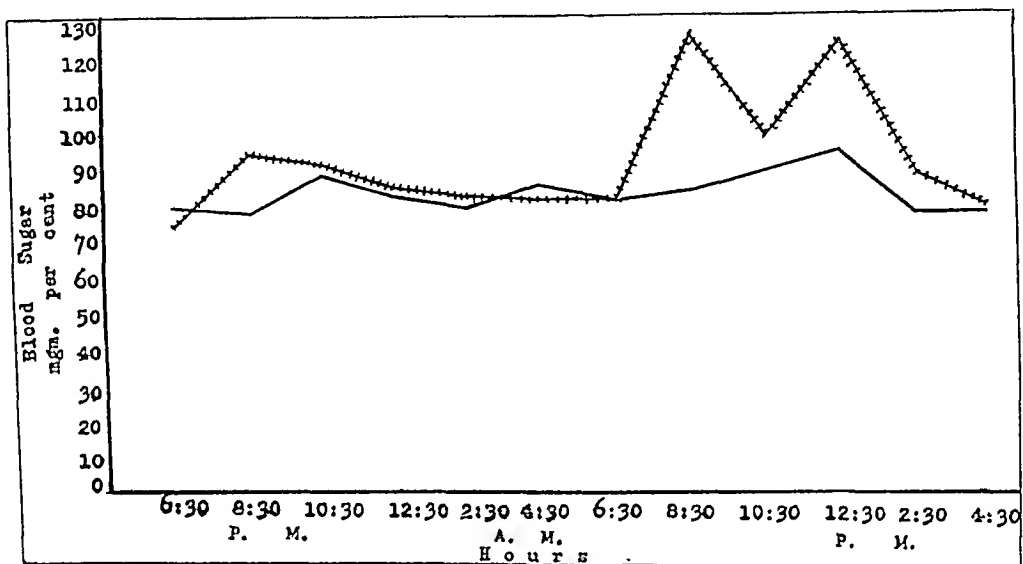


Chart 3.—Average two-hourly blood sugar variations in fasting and nonfasting normal persons over a period of twenty-four hours.

Two-Hourly Variations in Blood Sugar over a Period of Twenty-Four Hours in Fasting and Nonfasting Normal Persons

Subject	Fasting											
	P. M.				A. M.				P. M.			
	6:30	8:30	10:30	12:30	2:30	4:30	6:30	8:30	10:30	12:30	2:30	4:30
1	87	85	77	80	80	78	87	80	95	111	76	83
2	91	73	105	83	74	89	80	74	82	93	78	87
3	73	82	87	83	80	89	80	95	87	71	80	70
4	70	74	83	80	80	89	85	83	90	91	74	69
Subject	Nonfasting											
	6:30	8:30	10:30	12:30	2:30	4:30	6:30	8:30	10:30	12:30	2:30	4:30
	80*	91	89	82	86	80	75	133†	81	141‡	89	77
	65	87	87	83	78	95	80	138	111	125	80	71
	83	98	105	85	82	76	83	133	111	108	87	80
	69	95	83	83	82	75	83	100	89	122	95	83

* Food taken immediately after specimens of blood were taken.

† Breakfast taken about 8 a. m.

‡ Lunch taken about 12:10 p. m.

2. Sweeney, J. Shirley: Dietary Factors that Influence the Dextrose Tolerance Test, *Arch. Int. Med.* **40**:818 (Dec.) 1927.

insulin. With this knowledge interpretation of the observed changes becomes apparent. At the time the morning food is taken, the pancreatic tissue that has to do with carbohydrate metabolism has been at rest. There has been no stimulation. The effect, therefore, is the same as that observed in fasting persons,² namely, a sharp rise in blood sugar due to a sluggish endogenous insulin response. The noon meal is followed by a slightly more active response, and by the time the evening meal is taken, the response becomes more active—as in the case of persons who have been taking meals rich in carbohydrates²—and the blood sugar rises to a much lower figure as compared to the morning and noon levels.

The practical significance of these observations is obvious and confirms the conclusions of Jonas and his associates. In very mild diabetes, the blood sugar curve should be kept within normal limits by a single dose of insulin before breakfast. Owing to the “natural” tendency of the blood sugar to rise, this is the safest time for the administration of insulin. By the same reasoning, insulin reactions should be expected to occur in the afternoon or early evening, which is well known to be true by those who treat many diabetic patients.

Deductively, totally or almost totally diabetic patients would have to be treated by several injections of insulin at twenty-four hour intervals. This likewise is a common observation to those who treat patients with diabetes. It follows, therefore, that in treating patients with diabetes one can and should take an optimum advantage of the remaining functioning insulin-producing pancreatic tissue. This can be done with economic and functional advantage to the patient.

CONCLUSION

Twenty-four hour blood sugar curves were made for fasting and nonfasting normal persons. By these studies are explained certain observations noted in the handling of diabetic cases.

It is suggested that by taking into account the normal variations of the blood sugar curve, diabetic patients may be more accurately, satisfactorily and economically controlled.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

I. THE EFFECT ON BASAL METABOLISM OF REST AND OF THE DAILY ADMINISTRATION OF ONE DROP OF COMPOUND SOLUTION OF IODINE *

WILLARD OWEN THOMPSON, M.D.

Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School

ALLEN G. BRAILEY, M.D.

PHEBE K. THOMPSON, M.D.

AND

EDWARD G. THORP, M.D.

BOSTON

The normal daily requirement of the body for iodine has never been determined. Indirect evidence on the question is offered by analyses for iodine of soil, water, air and various foodstuffs as they occur in different parts of the world.¹ The foods richest in iodine are certain sea foods, but even these contain only from 0.07 to 2.4 mg. per kilogram, and most foods in the average dietary contain much less. McClendon and Williams² found that even in those districts of the United States in which the drinking water is relatively rich in iodine, it would be necessary to drink 10 liters of water daily in order to take in 0.10 mg. of the element by this means.

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* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

* A preliminary report of this work has already been published (Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exophthalmic Goiter, *J. A. M. A.* **91**:1719 [Dec. 1] 1928).

1. McClendon, J. F.: The Distribution of Iodine with Special Reference to Goiter, *Physiol. Rev.* **7**:189, 1927. Von Fellenberg, T.: Untersuchungen über das Vorkommen von Jod in der Natur: VII. Ueber der Jodgehalt der Gesteine, der geologischen Formationen und der Mineralien und über die Bedingungen der Jodaureicherung in Erden, *Biochem. Ztschr.* **152**:153, 1924. Von Fellenberg, T.: Distribution and Circulation of Iodin, *Schweiz. med. Wchnschr.* **55**:53, 1925. Von Fellenberg, T.: Untersuchungen über das Vorkommen von Jod in der Natur: V. Untersuchungen über den Jodgehalt der Luft, *Biochem. Ztschr.* **152**:135, 1924. Bourcet, P.: Recherche et dosage colorimetrique de petites quantités d'iode dans les matières organiques, *Compt. rend. acad. d. sc.* **128**:1120, 1899. Tressler, D. K., and Wells, A. W.: U. S. Bureau of Fisheries, Document 967, 1924.

2. McClendon, J. F., and Williams, A.: Simple Goiter as a Result of Iodine Deficiency; Preliminary Paper, *J. A. M. A.* **80**:600 (March 3) 1923.

McClendon and Hathaway³ and von Fellenberg⁴ have made valuable measurements of the ingestion and excretion of iodine in normal persons. The first observers, in a three day study of a normal subject, aged 23 years, found that on the average he took in 0.019 mg. and excreted 0.007 mg. of iodine per day. Von Fellenberg did a complete iodine metabolism study on himself, covering a period of fifty-four days. He even analyzed his sweat and nasal secretion for iodine. He maintained himself in iodine balance for twenty-eight days on a daily intake of 0.014 mg., but retained iodine when the intake was increased.

Boothby and co-workers⁵ maintained the basal metabolic rate of a "thyroidless individual" at a standard normal level by an average daily intravenous dose of 0.25 mg. of thyroxin, an amount which contains 0.16 mg. of iodine. Certain considerations make it appear probable, however, that this amount of iodine is not necessary to maintain the thyroid gland of a normal man in a healthy condition.⁶ The actual dose of thyroxin given was not 0.25 mg. daily, but an average of various doses given at intervals of from two to fourteen days. Some of the injected thyroxin was thus probably destroyed or excreted before it could affect the metabolism, and there is the possibility that iodine atoms from the catabolism of thyroxin are salvaged from the blood by the thyroid and built again into thyroxin molecules. Only in this way would it appear possible for the thyroid gland, particularly in regions where the iodine supply is low, to elaborate the large excess of thyroxin presumably present in exophthalmic goiter.

From a consideration of this evidence, it seems fair to assume that most normal people can maintain a healthy state with respect to thyroid function on a daily intake of iodine which certainly does not exceed, and is probably much less than, the 0.16 mg. of iodine which Boothby and co-workers found sufficient in the form of thyroxin.

In comparison with the almost minute physiologic requirement of iodine in normal persons, the dosage for exophthalmic goiter recom-

3. McClendon, J. F., and Hathaway, J. C.: Iodine Metabolism on Normal Diet in Relation to Prevention of Goiter, *Proc. Soc. Exper. Biol. & Med.* **21**:129, 1923.

4. Von Fellenberg, T.: Untersuchungen über dem Jodstoffwechsel: I. Versuche mit physiologischen Jodmengen beim Erwachsenen, *Biochem. Ztschr.* **142**:246, 1923.

5. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, *Tr. A. Am. Phys.* **40**:195, 1925.

6. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, *J. Clin. Investigation* **7**:437 (Aug.) 1929.

mended by Plummer⁷ in 1923 and by Plummer and Boothby⁸ in 1924 and widely used since that time in clinics both here and abroad, seems enormous. The drug has usually been given in the form of compound solution of iodine or potassium iodide, in amounts equivalent to 100 to 400 mg. of iodine per day, i. e., at least from 600 to 2,600 times the normal requirement. Observations on the effects of smaller doses seem to be rare. Neisser,⁹ in 1920, reported clinical improvement in a few patients with exophthalmic goiter during the administration of as small a dose as from 2 to 5 drops of a 5 per cent solution of potassium iodide three times daily (roughly, from 15 to 38 mg. of iodine daily). His usual routine was to begin with a dose of from 2 to 5 drops three times a day and increase the dose to an "optimum"—sometimes as much as 20 drops three times a day (about 153 mg. of iodine daily). One year later, Loewy and Zondek¹⁰ reported clinical improvement in a few cases from the use of as small a dose as 3 drops of a 5 per cent solution of potassium iodide three times daily (about 23 mg. of iodine daily). In three of their cases they confirmed their clinical impressions with determinations of the basal metabolic rate, although the size of the dose in these three cases is unknown. They usually began treatment with 3 drops of a 5 per cent solution of potassium iodide three times a day and increased the dose to 30 to 40 drops three times a day. Jagić and Spengler,¹¹ in 1924, reported on the treatment of sixteen thyrotoxic patients with 3 drops of a 5 per cent solution of sodium iodide three times a day (about 25 mg. of iodine per day). In eight patients the condition improved and in two became worse. Cowell and Mellanby,¹² in 1924, stated: "We have not yet determined the minimum quantity of iodide (potassium iodide) that will exert a demonstrable effect, but it is less than half a grain (about 25 mg. of iodine) daily." Cattell,¹³ in 1926, recommended that smaller doses than the customary ones be used, and said that 10 minims (0.6 cc.) of compound solution of iodine per day (about 84 mg. of iodine) had proved as satisfactory as larger amounts at the Deaconess Hospital in Boston.

7. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, Society Proceedings, J. A. M. A. **80**:1955 (June 30) 1923.

8. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66, 1924.

9. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, Berl. klin. Wchnschr. **57**:461, 1920.

10. Loewy, A., and Zondek, H.: Morbus Basedowii und Jodtherapie, Deutsche med. Wchnschr. **47**:1387, 1921.

11. Jagić, N., and Spengler, G.: Weitere Beobachtungen über Jodwirkung bei Strumen, Wien. klin. Wchnschr. **37**:116, 1924.

12. Cowell, S. J., and Mellanby, E.: The Effect of Iodine on Hyperthyroidism in Man, Quart. J. Med. **18**:1, 1924-1925.

13. Cattell, R. B.: The Elimination of the Iodine in the Urine in Normal Persons and in Exophthalmic Goiter, Boston M. & S. J. **195**:69, 1926.

Wahlberg,¹⁴ in 1926, reported a series of twenty cases in which he gave potassium iodide in doses of from 0.0025 to 0.015 Gm. three times a day (from about 6 to 34 mg. of iodine daily). He obtained a definite remission of the disease in six patients on 0.0075 Gm. three times a day (about 17 mg. of iodine daily). Of these, three were listed as severe, two as moderately severe and one as mild. His tables give no clear evidence that smaller doses were ever effective or that doses twice as large produced remissions when 17 mg. of iodine daily had failed.

In view of the fact that iodine remissions have been produced by doses of such varying size, it seemed desirable to determine, if possible, the range of effective iodine dosage in exophthalmic goiter. We arbitrarily chose to begin with a study of the effect of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily, as even this dose contained what appeared to be a large excess. Since this produced in most cases a maximum reduction in the basal metabolic rate, it was decided to go from this to smaller doses in geometrical progression ($\frac{1}{2}$ drop, $\frac{1}{4}$ drop, etc.). In the present paper we shall consider the effect of 1 drop daily and of larger doses.

METHOD

We observed the effect on basal metabolism of the administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily to seventeen unselected patients with exophthalmic goiter who were in the hospital being prepared for operation. Throughout the period of observation, determinations of basal metabolism were made at frequent intervals, usually daily. The routine procedure was to wait until a resting level of basal metabolism was reached. One drop¹⁵ of compound solution of iodine was then administered daily in the metabolism laboratory. When the metabolism again reached a level, much larger doses (usually 30 drops daily) were given. This was done in order to see if any further reduction in basal metabolism would occur, and to prepare the patient more adequately for operation. It is not a method of comparing the effect of large doses with that of small doses. This is shown by the fact that in three of the cases in this paper (charts 2, 3 and 5) the basal metabolism, after showing its maximum reduction on 1 drop daily, began to rise a little; this rise

14. Wahlberg, J.: *Das Thyreotoxikosesyndrom und seine Reaktion bei kleinen Joddosen*, Helsingfors, Mercators Tryckeri Aktiebolag, 1926.

15. Due to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. When this solution is kept in a corked bottle, a reaction takes place between it and the cork, as a result of which the cork is slowly destroyed and the solution becomes pale.

continued after the dose was increased to 20 to 30 drops daily. Furthermore, the administration of small doses may interfere with the effect of larger doses administered immediately afterward, as is suggested by the data on the effect of $\frac{1}{4}$ drop daily in a subsequent paper.¹⁶

We also observed the effect on basal metabolism of administering 1 drop of compound solution of iodine daily to twenty-three outpatients with exophthalmic goiter. Twelve of these had the disease in mild or in moderately severe form and had received no other treatment. Two had had roentgen treatment for several years before iodine was given. The remainder were patients who had thyrotoxicosis following a thy-

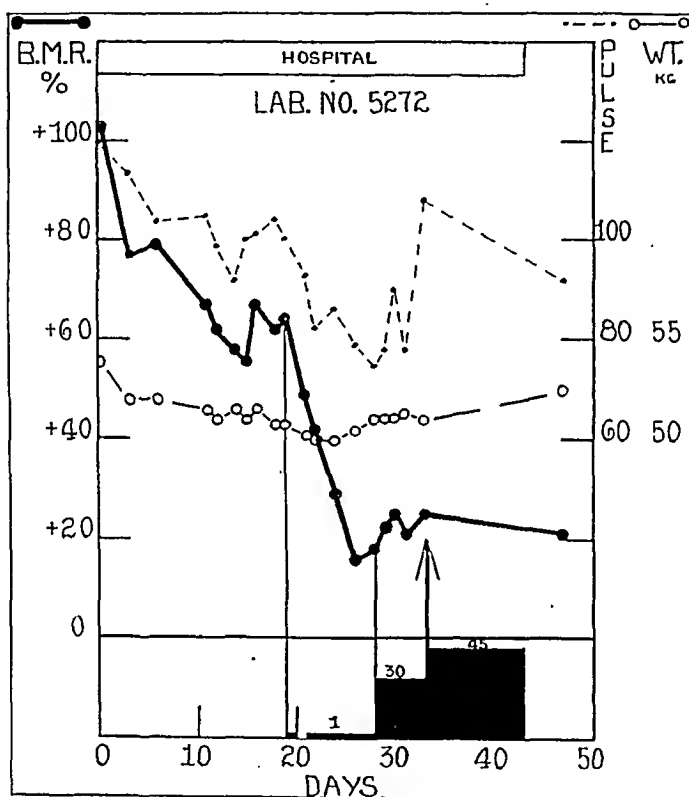


Chart 1.—Marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts, arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, the figures above them showing the dosage in drops.

roidectomy (usually subtotal). In no case was medication started or the dosage changed until the existing metabolic level had been confirmed by two or more tests which checked satisfactorily.

16. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of $\frac{1}{4}$ Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, *Arch. Int. Med.*, to be published.

The Benedict-Roth apparatus and Aub-DuBois standards were used in the determinations of the basal metabolism.

DATA

The results are summarized in tables 1, 2 and 3.

From table 1, it may be seen that in fifteen of seventeen patients (88 per cent) at rest in bed in a hospital, a reduction in basal metabolism of more than 10 per cent was noted during the administration of 1 drop of compound solution of iodine daily. In fourteen of the seventeen

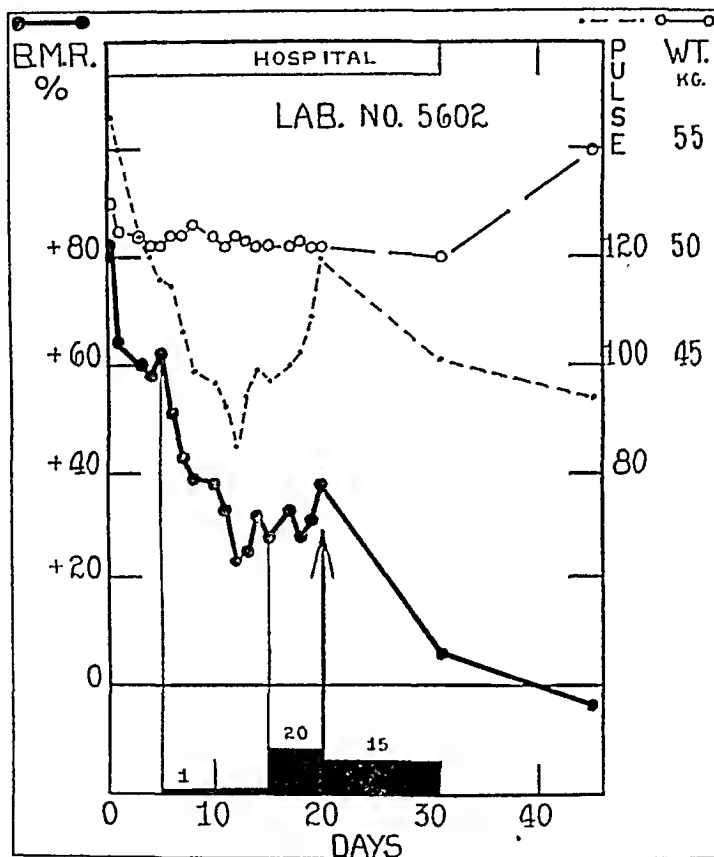


Chart 2.—Well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 20 drops daily, preceding subtotal thyroidectomy for exophthalmic goiter. In this and charts 3 and 5, a slight rise appeared to start shortly after the maximum reduction in basal metabolism on 1 drop, and to continue on the large dose.

patients, the effect of much larger doses was also noted. In thirteen of these as great a reduction in basal metabolism was obtained with 1 drop daily as with larger doses administered immediately afterward, while one patient showed a greater response during the administration of larger doses. The two that showed no reduction on 1 drop daily did not respond to 30 drops daily. This comparison of the effect of

TABLE 1.—Summary of the Consecutive Effects of Rest, the Daily Administration of One Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward, in Hospital Patients with Exophthalmic Goiter

Patient	Admission			Rest			On 1 Drop Compound Solution of Iodine Daily										On Larger Doses					Estimated Weight of Thyroid Gland at Time of Operation, Gm.				
	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolism, Points	No. of Days Before Testing Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolism, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Day	Drop in Basal Metabolism Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolism, Points		Length of Time Effect Was Observed, Days	Size of Dose in Drops, Daily	Total Change in Basal Metabolism, Points	
Mr. J. D.A.	4854	33	165	44	98	54.6	-17	3	9	+19	18	54.9	-25	8	1	7	7	2	15	93	44.0	-12	0	30	-27	95
Mr. P. O.L.	4888	48	174	+49	123	45.5	-8	1	5	+34	91	44.9	-15	9	3	0	0	0	+22	100	50.5	-1	15	30-30	-10	95
Mrs. C. G.	4893	49	168	+26	104	51.6	-12	1	5	+19	94	50.9	-7	8	0	0	0	0	+16	100	50.5	-3	10-30	-10	91	
Miss H. R.	4909	17	167	+40	104	59.7	-36	2	3	+20	102	57.1	-20	11	1	5	9	9	+21	108	57.0	+1	3	30	-19	216
Mrs. T. P.	4919	56	149	+30	106	51.7	-7	1	2	+8	80	50.2	-22	13	4	0	0	12	+0	108	57.0	+	4	30	-25	40
Mrs. E. G.	4958	53	187	+25	76	50.6	-16	3	8	+5	85	49.9	-30	9	1	0	0	5	+	59	49.8	+	4	30	-25	40
Mrs. L. DeN.	5059	25	144	+44	105	39.6	-13	3	6	+20	72	67.2	-24	6	4	0	7	8	+27	82	67.9	+	7	20	-31	98
Mrs. E. H.	5168	26	164	+58	109	69.5	-23	2	9	+16	77	51.1	-46	10	3	0	9	7	+23	88	51.1	+1	5	30	-40	98
Mrs. E. M.	5272	35	166	+63	99	50.8	-40	11	19	+17	78	44.6	-34	11	2	0	6	9	+25	75	45.6	+	15	15	-35	85
Mrs. A. B.	5119	28	156	+103	120	53.9	-16	1	6	+26	84	44.0	-27	10	1	0	6	6	+29	69	68.0	+	10-30	-17	85	
Mr. W. B.	5475	33	159	+49	106	62.5	-15	2	8	+0	68	66.1	-49	18	2	0	11	11	+2	89	43.7	+	4	30	-20	221
Mrs. B. W.	5191	44	154	+49	111	45.1	-6	0	3	+22	84	44.0	-27	10	1	0	6	6	+46	129	44.1	+	7	20	-36	221
Miss V. G.	5581	18	160	+82	122	47.4	+2	0	4	+47	124	44.4	-35	9	1	0	5	5	+27	81	48.4	+	3	30	-29	54
Mr. H. E.	5596	33	172	+56	101	47.7	+2	0	2	+27	80	47.7	-29	12	1	11	10	7	+31	104	50.5	+	5	20	-29	54
Mrs. M. McO.	5602	28	160	+60	120	50.4	-22	1	5	+22	94	50.5	-38	10	1	10	4	4	+8	80	45.8	+	2	30	-29	80
Mrs. A. F.	5656	45	152	+37	95	44.1	+7	0	7	+10	80	45.7	-27	10	1	0	4	0	+15	112	57.7	-2	5	30	-2	..
Mrs. A. H.	5741	50	153	+17	108	56.7	-19	4	20	+17	116	57.4	0	9	0	0	0	0	+	112	57.7	-2	5	30	-2	..
All patients (17)....																										
All who received large doses (14)....																										
All in whom the basal metabolic rate dropped 10 points or more (15)....																										
Average																										
All in whom the basal metabolic rate dropped 10 points or more and who received large doses (12)....																										
+67																										
+52																										
-15																										
+20																										
-32																										
11																										
+22																										
+2																										
6																										
-27																										
-30																										

TABLE 2.—Detailed Presentation of the Data on Basal Metabolism Summarized in Table 1 *

Patient	Lab. No.	Days Before Starting Iodine										Days After Starting Iodine																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Mr. J. D'A.	4854..	A	+61	+45	+39	+33	+18	+22	+13	+24	+19	+18	+33†	S	
Mr. P. O'L.	4888..	A	+57	+48	+45	+53	+49	+46	+38	+47	+36	+28	+33	+38†	+27	+28	+28	+19	+27	
Mrs. C. G.	4893..	A	+38	+26	+20	+31	+22	+20	+20	+18	+17	+19	+17†	+15	+16	S	+21	
Miss H. R.	4909..	A	+76	+38	+42	+37	+32	+31	+26	+26	+25	+23	+18	+17	+23†	+21	S+20	
Mrs. T. P.	4949..	A	+37	+28	+32	+30	+29	+25	+19	+13	+6	+9	Iodine omitted	
Mrs. E. G.	4958..	A	+41	+22	+34	+19	+14	+8	-3	-1	-8†	±0	S±0	
Mrs. L. DeN.	5059..	A	+57	+51	+45	+50	+38	+43	+40	+38	+18	+21	S	
Mrs. E. H.	5103..	A+81	+63	+52	+58	+53	+59	+50	+53	+38	+24	+11	+19	+16†	+20	+23	+26	+35	+30	S+29	
Miss E. M.†	5272..	+67	+62	+58	+56	+67	+62	+61	+49	+42	+29	+16	+18†	+22	+25	+21	S+25	
Mrs. A. B.	5419..	A	+76	+62	+56	+60	+63	+58	+56	+44	+39	+36	+23	+27	+25	+30	+27	+25†	+27	+21	+25	S+21	
Mr. W. B.	5475 A	+64	+69	+49	+49	+50	+50	+47	+48	+35	+29	+20	+16	+13	+11	+8	+5	+4	+2	-3	+1	+2†	-1	
Mrs. B. W.	5491..	A	+55	+47	+50	+49	+40	+37	+30	+26	+22	+20	+22	+25†	+27	+26	+33	S+31	
Miss V. G.	5531..	A	+80	+88	+78	+49	+45†	+23	+50	+42	RII	
Mr. H. E.	5596..	A	+54	+59	+56	+15	+11	+31	+21	+22	+19	+25	+33	+39	+27†	+27	+28	S+27
Mrs. M. McO.	5602..	A	+82	+61	+69	+59	+61	+51	+43	+39	+48	+33	+23	+25	+32	+28†	+33	+28	+31	S+38
Mrs. A. F.	5656..	A	+30	+26	+36	+37	+25	+27	+10	+14	+12	+8	+8	+10†	+10	+6	S+28	
Mrs. A. H.‡	5741 Sore throat	+21	+18	+22	+23	+25	+19	+25	+13	+23	+17	+17†	+19	+15	+16	+14	S

* A represents the time of admission to the hospital; S, subtotal thyroidectomy, and RII, right hemithyroidectomy.

† The time of starting larger doses (usually 30 drops daily).

‡ Admission was on the 21st day; the basal metabolic rate was +103, +77 and +79 on the 20th, 17th and 14th days, respectively, before starting iodine. The dose of iodine was gotten on the second day.

§ Admission was on the 22d day; the basal metabolic rate was +36, +28, +19, +20, +13, +12 and +15 on the 21st, 10th, 17th, 16th, 15th, 13th and 12th days, respectively, before starting iodine.

TABLE 3.—Summary of the Effects of the Daily Administration of One Drop of Compound Solution of Iodine, and of Larger Doses Given Immediately Afterward, to Outpatients with Exophthalmic Goiter

Patient	Lab- ora- tory No.	Height, Age Cm.	Before Treatment		After Reaching Level on One Drop of Compound Solu- tion of Iodine Daily			After Reaching Level on Larger Doses			Total Change in		Comment
			Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Change in Basal Meta- bolic Rate, Points	Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Change in Basal Meta- bolic Rate, Points	Basal Meta- bolic Rate Doses, Points				
Miss E. D.	316	52	154	+46	91	55.5	+4	67	59.9	-12	Roentgen treatment several years before Following subtotal thyroidectomy.
Mr. J. W.	1812	44	174	+17	92	55.6	-2	73	55.7	-19	Roentgen treatment several years before Following subtotal thyroidectomy.
Mr. F. B.	2265	11	150	+39	108	32.8	+4	87	32.7	-35	Following subtotal thyroidectomy
Mr. O. G.	2375	32	171	+39	86	65.4	+21	64	67.7	-18	Following subtotal thyroidectomy
Mrs. M. R.	3913	24	159	+30	76	48.1	+1	68	48.5	-20	Following subtotal thyroidectomy
Mrs. C. N.	3961	30	159	+28	98	44.2	+6	93	46.8	-22	Following subtotal thyroidectomy
Miss B. P.	3937	16	148	+20	112	52.4	-2	81	53.7	-22	Following subtotal thyroidectomy
				+12	105	52.6	-10	78	53.8	-22	Preceding operation
Mrs. E. O.	4675	35	156	+29	106	47.7	+1	83	48.7	-23	Following subtotal thyroidectomy
Miss E. F.	4694	28	172	+23	83	68.0	-2	72	72.9	-25	No other treatment
Mrs. I. G.	4758	38	159	+29	103	63.0	+2	81	66.1	-27	Preceding operation
				+19	90	72.1	+10	92	69.1	-9	Following subtotal thyroidectomy
Miss A. Y.	4822	21	165	+72	133	51.7	+28	91	53.0	-44	Preceding operation
				+67	118	52.7	+34	93	53.8	-33	No other treatment
Mrs. E. F.	4906	28	158	+21	83	45.5	-1	64	45.7	-22	No other treatment
Miss E. K.	4935	17	152	+15	100	43.5	+15	94	44.2	-9	No other treatment
Mrs. G. G.	4986	25	147	+21	93	62.1	+0	68	63.5	-21	Following subtotal thyroidectomy
Miss S. G.	5092	18	148	+40	124	42.9	+26	96	43.9	-14	No other treatment
Mrs. E. H.	5168	27	161	+44	107	88.5	+8	74	92.0	-36	Following subtotal thyroidectomy
Miss E. M.	5272	35	166	+43	94	61.3	+23	74	64.5	-20	Following subtotal thyroidectomy
Miss F. W.	5530	15	157	+14	120	44.8	-1	84	47.5	-15	No other treatment
				+17	104	45.8	+7	97	47.7	-10	No other treatment
Mr. E. D.	5663	49	160	+26	89	56.3	-16	70	63.5	-42	No other treatment
Mr. I. O.	5667	41	167	+51	108	70.9	+46	102	70.8	-5	Preceding operation
				+19	87	68.1	+30	86	74.3	+11	Following subtotal thyroidectomy
Mr. E. S.	6251	35	164	+50	100	55.5	+15	78	53.6	-35	Preceding operation
Mr. A. B.	6312	35	171	+29	101	52.3	+28	100	56.9	-1	Preceding operation
Mrs. E. R.	6414	34	161	+42	82	52.4	+19	68	53.5	-23	Preceding operation
Average													...
All observations (28)....			+32	+11	-21	
All receiving large doses (15).....			+30	+8	-22	
All in whom basal meta- bolic rate dropped 10 points or more (23)....			+33	+7	-26	
All in whom basal meta- bolic rate dropped 10 points or more and who received large doses (13).....			+31	+6	-25	

the small dose with that of the large dose is perhaps not entirely reliable, as the large dose may have been given for too short a time to produce its maximum effect.

For all seventeen patients, the average level of basal metabolism just after admission to the hospital was plus 60 per cent; after a period of rest, it was plus 46 per cent, and after 1 drop of compound solution of iodine daily had had its maximum effect, it was plus 19 per cent. The corresponding figures for the fourteen cases in which observations were also made on larger doses given immediately afterward, were plus 62, plus 48 and plus 19 per cent; and the average basal metabolism on larger doses was plus 21 per cent (table 1).

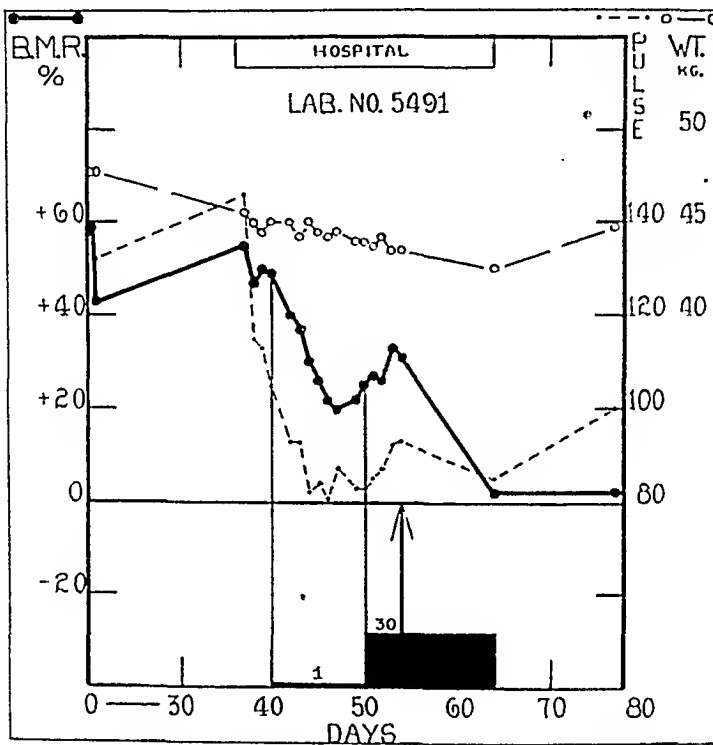


Chart 3.—Well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

From table 3 it may be seen that in twenty-three of twenty-eight observations (82 per cent) on the effect of administering 1 drop of compound solution of iodine daily to twenty-three outpatients, a reduction in basal metabolism of more than 10 per cent was noted. The average level of basal metabolism was plus 32 per cent before iodine was started and plus 11 per cent after 1 drop daily had had its maximum effect. In fifteen observations in which the effect of larger doses (2 to 45 drops daily) given immediately after the small dose was noted, the corresponding figures were plus 30 and plus 8 per cent, and the average

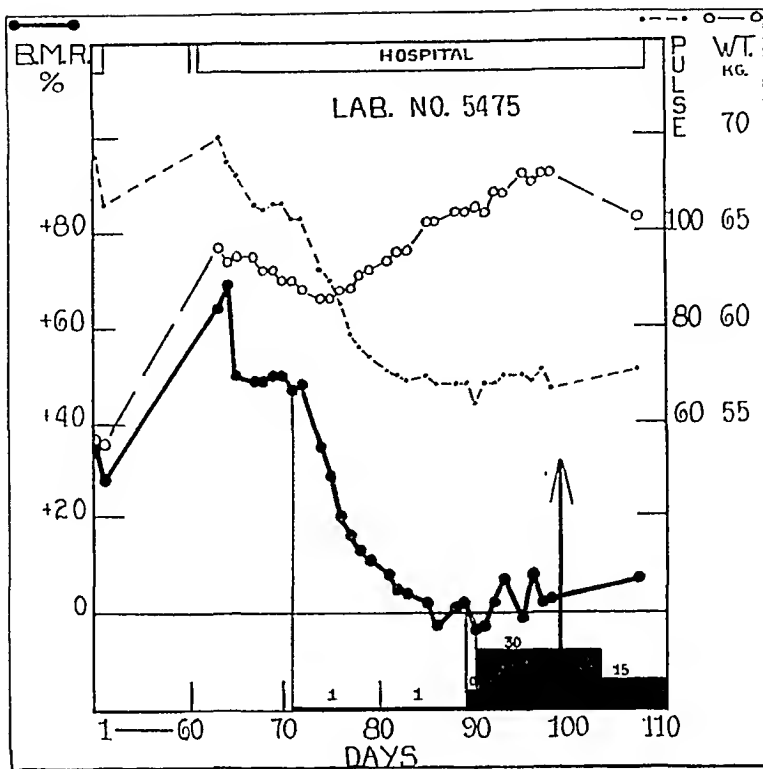


Chart 4.—Marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

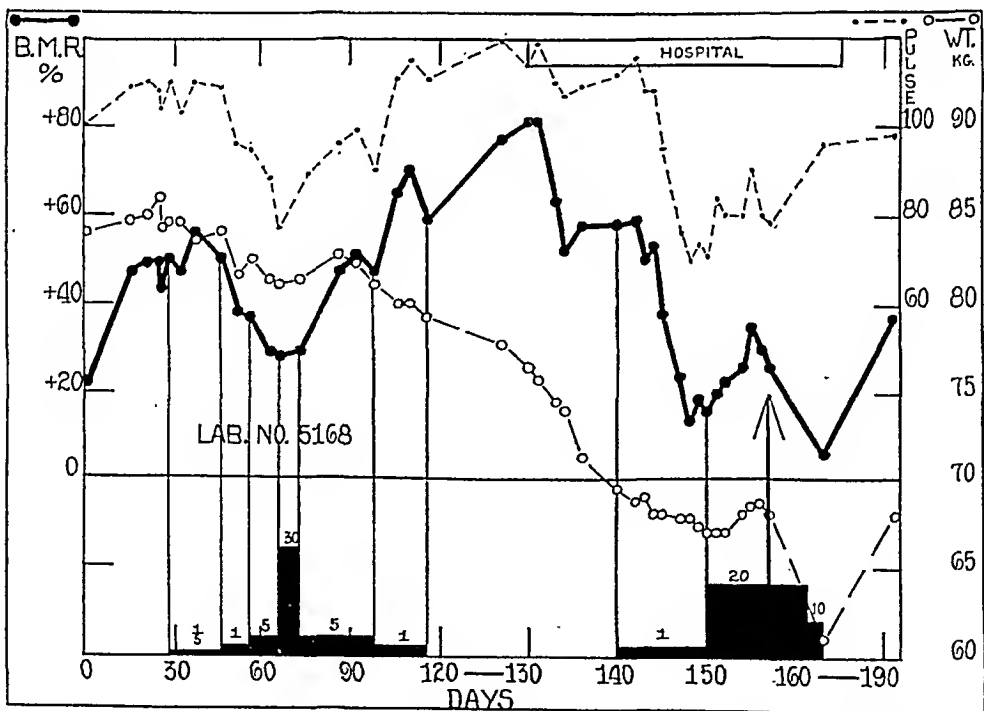


Chart 5.—The effect of slowly increasing and decreasing the dose of iodine. Note that the patient became partially refractory to 1 drop of compound solution of iodine daily while in the outpatient department but that after a short period of omission of iodine she showed a marked reduction in basal metabolism on this dose while in the hospital.

basal metabolism after the larger doses had produced their effect was plus 8 per cent. In three of these observations (20 per cent) the basal metabolism was slightly lower (9 to 12 points) during the administration of larger doses than during the administration of 1 drop daily.

Data on typical individual house cases are recorded in charts 1 to 5, and on an individual outpatient in chart 6.

Starr, Segall and Means,¹⁷ in 1924, reported that the effect on basal metabolism of the administration of 15 drops of compound solution of iodine daily in exophthalmic goiter, was as great in 48 per cent of their series (eight cases) as the immediate effect of removal of five sixths of the thyroid gland in ten cases studied by Segall and Means¹⁸

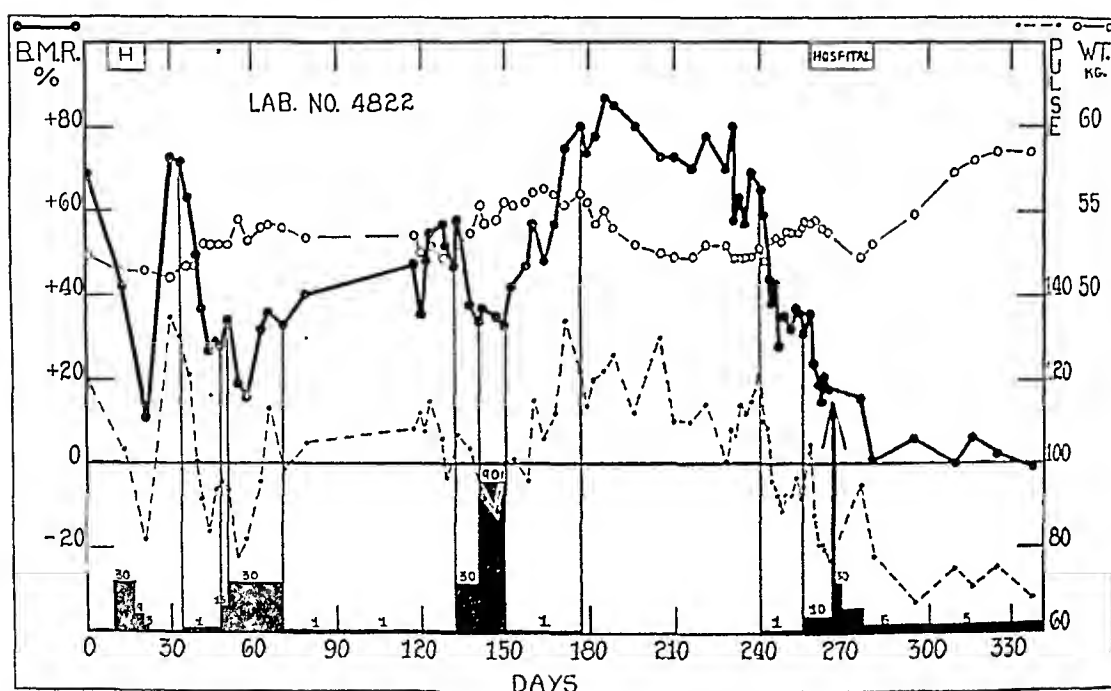


Chart 6.—Well marked reduction in basal metabolism on two occasions (second and third administrations of iodine) in an outpatient during the administration of 1 drop of compound solution of iodine daily. While the patient was slowly becoming completely refractory to 1 drop daily, the temporary administration of from 30 to 90 drops daily depressed the basal metabolism about 20 points below the level at which the small dose held it. Note that although the patient had become completely refractory to 1 drop a day, there was a marked reduction on this dose following a two months' period of freedom from iodine.

17. Starr, P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, *Arch. Int. Med.* **34**:355 (Sept.) 1924.

18. Segall, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter: Daily Basal Metabolism and Pulse Observations, *Arch. Surg.* **8**:176 (Jan.) 1924.

before the days of iodine. Composite curves of basal metabolism for both their groups of patients are reproduced in chart 8 and compared with a composite curve¹⁹ of basal metabolism (chart 7) for the ten of our seventeen hospital patients (59 per cent) who showed the greatest reduction in basal metabolism during the administration of 1 drop daily. The three curves practically coincide. This is evidence that the reduction in basal metabolism during the administration of 1 drop daily is as great as that during the administration of larger doses.

A GREATER REDUCTION IN BASAL METABOLISM ON LARGER DOSES

It is just as important to study the patients who required more than 1 drop daily to produce a maximum effect, as to study those who did not. Data on such cases are recorded in charts 5, 6, 9 and 10. The data in chart 9 are those of the hospital patient who showed a greater reduction on 30 drops daily than on 1 drop daily.

One of the most significant observations is perhaps the fact that the dose that will produce a maximum effect may vary in the same patient from time to time, evidently on account of a spontaneous variation in the disease. Owing to the same cause, apparently, the response to the same dose may vary in the same patient from time to time. This is shown in chart 10.²⁰ During the first administration of iodine, little reduction in basal metabolism was observed on 5 drops of compound solution of iodine daily. During the second administration, 1 drop daily had a marked effect, but the subsequent administration of 30 drops daily depressed the metabolism a little more. During the third administration, 1/5 drop daily was given first. It produced a moderate effect, and no further drop occurred on from 1 to 5 drops daily. Nevertheless, the response was less than during the second administration of iodine.

In charts 5 and 6 are presented data on a patient who became partially refractory and on one who became completely refractory, respectively, to a dose of 1 drop of compound solution of iodine daily during the continuous administration of iodine. After iodine was

19. This composite curve was obtained as follows: Working backward and forward from the point at which iodine was begun, we averaged the daily metabolisms of all patients. Where observations on any one patient at rest in bed or on 1 drop daily ended, each curve was stopped. The composite curve therefore, does not show adequately the reduction with rest in bed. In any patient in whom no determination of metabolism was made for one day, the level on this day was supposed to be at the point where the line connecting the determinations on either side crossed it.

20. The data on this case are being published in detail elsewhere (Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Temporary Myxedema During the Administration of Iodine in Exophthalmic Goiter, *Am. J. M. Sc.*, in press) to illustrate another point.

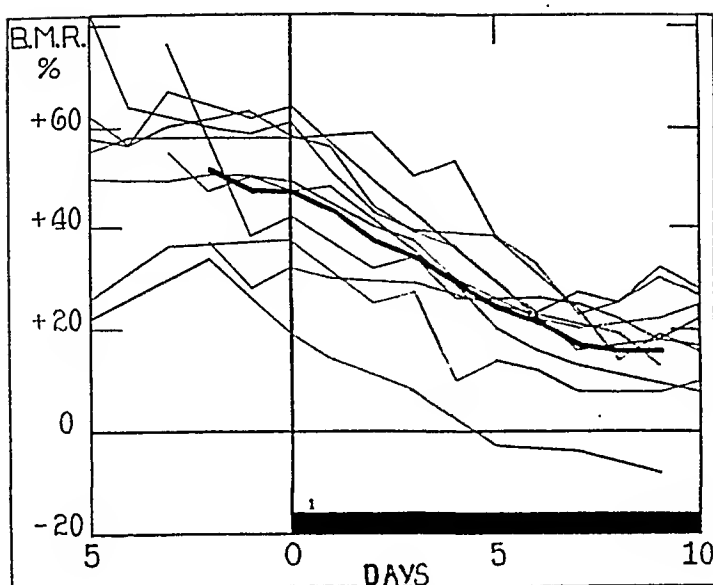


Chart 7.—Composite curve (heavy black line) showing the average rate of reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily in the ten of our cases (nos. 4909, 4949, 4958, 5168, 5272, 5419, 5475, 5491, 5602 and 5656) that showed the greatest response on this dose. The light black lines denote the course of the basal metabolism in individual cases. Cases 5581 and 5596, although showing slightly greater reduction in metabolism than two of the cases included, were omitted because of the infrequency of the observations in case 5581 and their variability in case 5596.

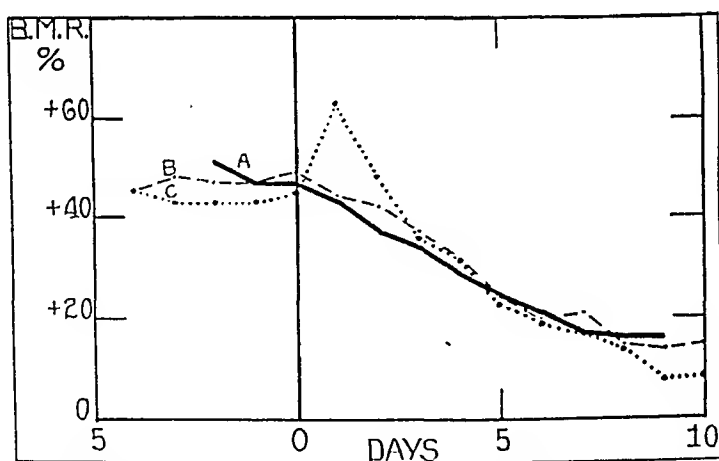


Chart 8.—A comparison of the composite curve of daily basal metabolism for our ten cases which showed the greatest reduction during the administration of 1 drop of compound solution of iodine daily (curve A is taken from chart 7) with that of Starr, Segall and Means for 48 per cent (eight cases) of their series in which 15 drops daily were given (curve B) and that of Segall and Means for ten cases in which the immediate effect of a subtotal thyroidectomy was noted (curve C). The vertical line denotes the point at which treatment was begun. Except for the immediate postoperative rise in C, the three curves practically coincide.

omitted for twenty-four days in the first instance, and for sixty-two days in the second instance, these patients showed a maximum reduction in basal metabolism during the administration of the dose to which they previously had been refractory, viz., 1 drop daily. In the second instance, while the effect of 1 drop of compound solution of iodine a day was slowly wearing off, the temporary administration of from 30 to 90 drops a day caused a reduction in basal metabolism from about plus 55 to about plus 35 per cent. In the first instance,²¹ iodine was first given in slowly increasing doses (1/5, 1, 5 and 30 drops daily) and then in slowly decreasing doses (30, 5 and 1 drop daily). There was no response to 1/5 drop and a maximum response on the first admin-

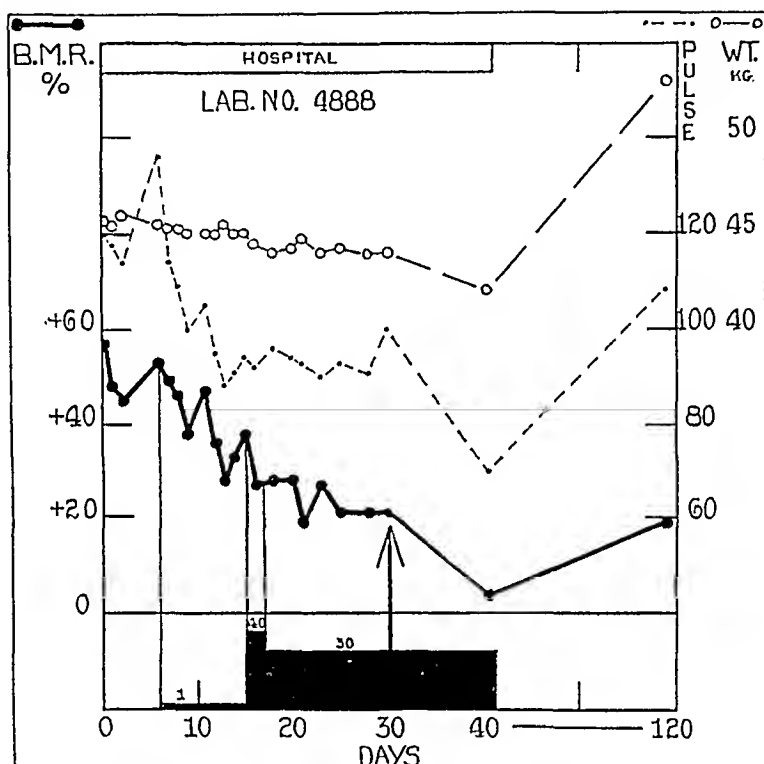


Chart 9.—A moderate reduction in basal metabolism during the daily administration of 1 drop of compound solution of iodine with a slight further reduction during the administration of from 30 to 40 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

istration of 5 drops. As the dose was decreased, the basal metabolism was higher on 5 drops and on 1 drop daily than it had previously been on these doses, and the disease was correspondingly more intense. The data suggest, but by no means prove, that during the period when the metabolism was rising during the administration of iodine, larger doses might have held it at a lower level than did 1 drop daily.

21. Most of the data on this case and some of the data on case 4822 are being published elsewhere (Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, *Arch. Int. Med.*, in press) to illustrate another point.

These two cases suggest that at stages of the disease in which the patient is becoming refractory to iodine, the effective range of iodine dosage may become placed at increasingly higher levels, until finally no response occurs. Under these circumstances we doubt if the effective dose ever exceeds 5 drops of compound solution of iodine daily. Lack of response to all doses is, of course, sometimes observed in patients who previously received none of this medication.

In cases 3961, 4675 and 4822 (outpatients) the basal metabolism was 9, 12 and 10 points lower, respectively, on larger doses than on 1 drop daily.

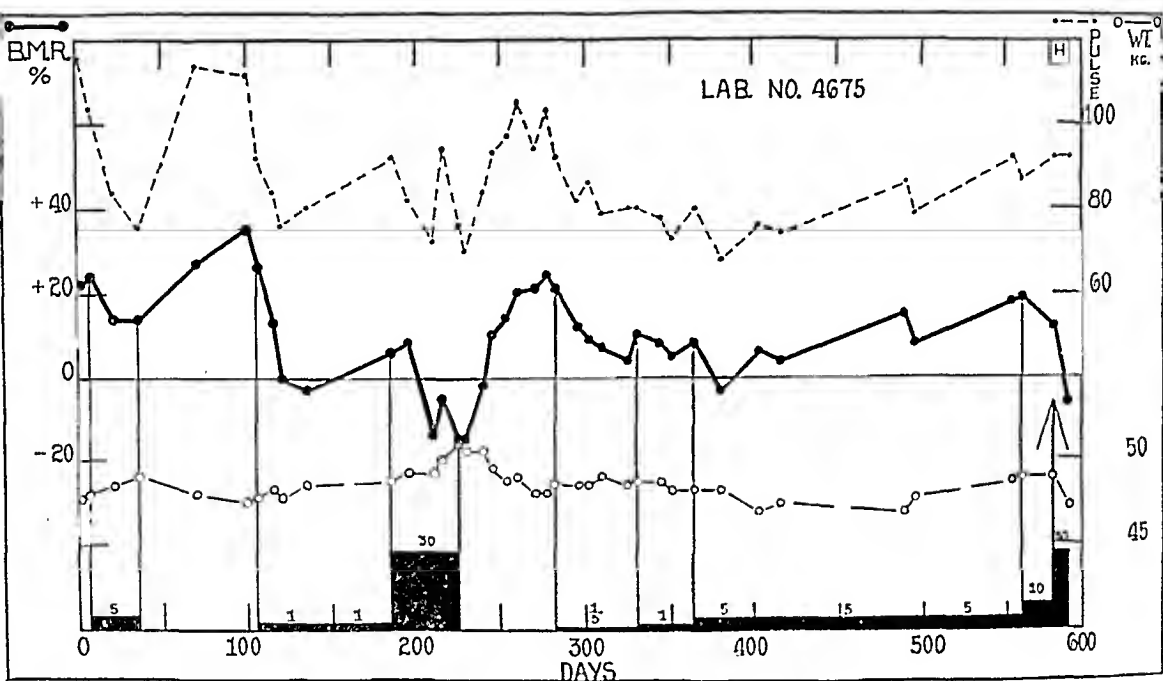


Chart 10.—Variations in the amount of iodine necessary to produce a maximum response, and in the magnitude of the reduction in basal metabolism during the administration of the same dose of iodine at different times to the same patient.

TIME REQUIRED FOR THE REMISSION PRODUCED BY 1 DROP DAILY

It may be seen from chart 8 that the reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily occurred just as quickly as the reduction during the administration of 15 drops daily. This would suggest that the speed of the reduction in basal metabolism is unaffected by the size of the dose so long as it is large enough to produce a maximum effect.

The average time required for the maximum effect to occur in our house patients was seven days. Thus, the average rate of reduction in basal metabolism for house patients who responded was 4.4 points per day. The time varied for the most part between five and eight

days. In one house patient (chart 4) it took fourteen days for the maximum effect to occur; in this patient the rate of decrease became markedly slower as the normal level of basal metabolism was approached.

In our outpatients who received 1 drop daily, observations were usually not made at sufficiently frequent intervals to enable us to determine when the maximum response appeared. In eight cases in which rough calculation was possible, however, it appeared to occur about as quickly as in the house patients.

As one would expect, marked individual variations were noted in the configuration of the curves denoting the drop in basal metabolism. In nine of fourteen cases in which calculation was possible, a drop had started within two days. In five cases it had started within twenty-four hours. A good example of the pronounced influence of this small dose of iodine may be seen in chart 1. In this patient, the dose was forgotten on the second day, yet within forty-eight hours following the administration of only 6 mg. of iodine the metabolic rate had dropped 16 points.

In four cases an interval of three to four days elapsed between the beginning of the administration and the onset of an effect on basal metabolism. This is illustrated well in chart 5. Plummer²² said that this lag often occurs.

Once the drop had started, it was usually rapid and often appeared to continue at a uniformly rapid rate until a maximum effect occurred, whereupon it stopped abruptly (seven cases). The rapidity of this decrease is not unlike the rapidity with which the basal metabolism drops from the high level produced by the oral administration of desiccated thyroid, on omission of this medication.²³ In three cases a level was reached for two to three days in the curve of descent, following which the basal metabolism appeared to drop as abruptly as previously. In four of the cases, the velocity of the reduction in basal metabolism appeared to decrease as the point of maximum effect was approached.

CONTROL OF REST

The data are recorded in table 1 of this paper, table 1 of the paper on the effect of $\frac{1}{2}$ drop,²⁴ and table 1 of the paper on the effect of $\frac{1}{4}$ drop.¹⁶

22. Plummer, H. S.: Personal communication to the author.

23. Aub, J. C., and Stern, N. C.: The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart-Block, *Arch. Int. Med.* **21**:130 (Jan.) 1918.

24. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of Half a Drop of Compound Solution of Iodine, *Arch. Int. Med.*, to be published.

If we had started iodine in our house patients following the initial determination of the basal metabolism and had not secured a resting level, our supposed decrease in this factor in our 1 drop, $\frac{1}{2}$ drop and $\frac{1}{4}$ drop series would have been about 50, 100 and 200 per cent greater, respectively, than it actually was. Thus it would have appeared that 1 drop reduced the basal metabolic rate 41 points (from plus 60 to plus 19 per cent) instead of 27 points (from plus 46 to plus 19 per cent); that $\frac{1}{2}$ drop reduced it 28 points (from plus 54 to plus 26 per cent) instead of 14 points (from plus 40 to plus 26 per cent); and that $\frac{1}{4}$ drop reduced it 28 points (from plus 62 to plus 34 per cent) instead of 9 points (from plus 43 to plus 34 per cent). All three doses would thus have appeared to have had a well marked effect on the basal metabolism, and a comparison of their effects would have been hopeless. The importance of securing a resting level of basal metabolism before administering iodine in any study of the effects of different doses or preparations is, therefore, obvious.

A question that naturally arises is whether the resting periods were long enough. As a rule, the basal metabolic rate dropped to a level in from one to six days. The observations of Sturgis²⁵ and of Kessel, Lieb and Hyman²⁶ suggest that this level may be maintained for several months. Sturgis noted the effect of rest in bed without other treatment in one patient for 134 consecutive days. The basal metabolism dropped from plus 107 to plus 47 per cent in eleven days and remained at the lower level for 123 more days, at which time operative procedures were begun. The average reduction which Kessel, Lieb and Hyman observed after one month (based on twenty-seven of the first thirty-eight patients reported) was 12 per cent (from plus 44 to plus 32 per cent)—which is roughly the same as Means and Aub²⁷ and we ourselves noted in from one to three weeks. It thus appears probable that the resting levels we determined would have persisted at least throughout the period covered by iodine medication. It is unfortunate that the data of Kessel, Lieb and Hyman are complicated by the administration of syrup of ferrous iodide after the fourth to the sixth week. It cannot be definitely stated, of course, that in our cases a further reduction would not have occurred from further rest alone. While in forty of the fifty-three patients the

25. Sturgis, C. C.: Observations on One Hundred and Ninety-Two Consecutive Days of the Basal Metabolism Food Intake, Pulse Rate and Body Weight in a Patient with Exophthalmic Goiter, *Arch. Int. Med.* **32**:50 (July) 1923.

26. Kessel, L.; Lieb, C. C., and Hyman, H. T.: Study of Exophthalmic Goiter and the Involuntary Nervous System: IX. An Estimation of the Pathogenesis and the Evaluation of Therapeutic Procedures in Exophthalmic Goiter, *J. A. M. A.* **79**:1213 (Oct. 7) 1922.

27. Means, J. H., and Aub, J. C.: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism with Remarks Concerning the Effect of Various Forms of Treatment, *J. A. M. A.* **69**:33 (July 7) 1917.

basal metabolic rate was at a level for more than three days before starting iodine, it was in only a few cases that more than six days elapsed from the time a level was reached until iodine was started. In one case no level was reached; in four the basal metabolism was the same for only two days, and in eight for only three days before starting iodine. In three cases in which the effect of rest (in bed) was noted for twenty, nineteen and eighteen days, the reduction in the basal metabolic rate continued for four, eleven and sixteen days respectively, and in one case in which it was noted for twelve days there was no reduction in metabolism. It would be important to know how much reduction in basal metabolism would have occurred had rest in bed been the only treatment employed for as long a period as that covered by rest and iodine medication in our series. The inconvenience to the patients and the expense of hospitalization for such an investigation are usually not justifiable. Until these data are actually recorded, however, the reduction in basal metabolism caused by any dose of iodine must remain somewhat uncertain.

In case 5168 (chart 5), 1 drop daily was insufficient to produce a maximum response while the patient was at home, but was adequate when she was in the hospital. In view of such data, one wonders whether the minimum dose required to produce a maximum effect sometimes may not be greater under conditions of activity than under conditions of rest. However, the disease may have varied spontaneously; and when the patient was an outpatient, the administration of 1 drop daily was preceded by the administration of $1/5$ drop daily, which, as the data on our $1/4$ drop series¹⁶ suggest, may have interfered with the effect of 1 drop.

COMMENT

From the data presented, it would appear that the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston is not greater than 6 mg. daily in the form of compound solution of iodine. From the data presented in subsequent papers,²⁸ it would also appear that it is not much less than 6 mg. daily. The relation of the size of the dose to the storage of colloid is discussed in the paper on the $1/4$ drop series,¹⁶ in which a general summary of our results to date is given.

Six milligrams of iodine a day is not recommended as a routine in the preparation of patients for operation. In fact, we think it is probably unwise to use a dose that is about adequate to produce a maximum reduction in the basal metabolic rate, but prefer one which supplies a marked excess. There is, moreover, some reason to suppose

28. Thompson, Cohen, Thompson, Thorp and Brailey (footnote 16). Thompson, Thorp, Thompson and Cohen (footnote 24).

that the effect of iodine in exophthalmic goiter cannot be measured entirely by the degree of depression of the basal metabolism.²⁹ It appears, however, that present doses are needlessly large and unpleasant. In particular, the huge doses (90 minims [5.6 cc.] or more) given in many clinics the day before, the day of and the day after operation are probably of no more value than much smaller doses. It has been satisfactorily demonstrated that iodine does not affect the increase in metabolism following the intravenous injection of thyroxin in rabbits³⁰ or the administration of thyroid by mouth in man.³¹ Iodine therefore presumably acts by producing changes in the thyroid gland. Probably all that it can do postoperatively is to control the thyrotoxicosis in the portion of thyroid gland not removed at operation. Since this portion is usually small, the amount of iodine required for this purpose would also appear to be small. As pointed out above, we doubt if good is ever done by giving more than 5 drops of compound solution of iodine daily. We think this probably would be adequate in the routine pre-operative and postoperative treatment of exophthalmic goiter, and see no reason why the dose should be increased at the time of operation.

Several observers³² are of the opinion that large doses of iodine sometimes may be more detrimental than small doses when the administration is long continued. This opinion is not based on adequately controlled data. In some experiences we have had with the prolonged treatment of exophthalmic goiter by iodine alone,³³ we have seen the condition grow worse after temporary improvement during the continuous administration of small doses (1 drop daily), just as during the continuous administration of large doses (from 15 to 30 drops daily). This has led us to believe that the percentage of cases of exophthalmic goiter which will respond satisfactorily to iodine for an indefinite period is probably little influenced by the size of the dose so long as it is large enough to produce a maximum effect. The problem can be definitely settled, of course, only by giving large doses

29. This opinion is also held by Dr. E. P. Richardson.

30. Sturgis, C. C.; Zubiran, S.; Wells, G. W., and Badger, T.: Effect of Iodine by Mouth on the Reaction to Intravenous Injections of Thyroxin, *J. Clin. Investigation* **2**:289, 1925.

31. Segall, H. N.: Unpublished data. Carson, D. A., and Dock, W.: The Effect of Iodin upon Experimental Hyperthyroidism in Man, *Am. J. M. Sc.* **176**: 701, 1928.

32. Cowell and Mellanby (footnote 12). Fraser, F. R.: Iodine in Exophthalmic Goitre, *Brit. M. J.* **1**:1, 1925. Cole, L. B.: The Use of Lugol's Iodine in Exophthalmic Goitre, *Lancet* **1**:812, 1927. Marine, D.: Iodin in the Treatment of Diseases of the Thyroid Gland, *Medicine* **6**:127, 1927. Beebe, S. P.: Iodine in the Treatment of Goiter, *M. Rec.* **99**:996, 1921.

33. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, *Arch. Int. Med.*, in press.

of iodine to one group of patients for a long time and small doses to another group for a long time. Large doses have a most unpleasant taste. For this reason alone, when iodine medication is to be long continued, it is desirable to use the smallest dose that will produce a maximum effect (usually 1 drop of compound solution of iodine daily). This applies especially to patients who have residual thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter³⁴ and to a few mild cases of the disease in which treatment with iodine alone may be given.

SUMMARY AND CONCLUSIONS

During the daily administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) to seventeen unselected hospital patients with exophthalmic goiter, fifteen showed a reduction of 15 to 49 points in basal metabolism, and two showed no change. The reduction appeared to be as great as that noted by other observers on much larger doses. A maximum decrease in basal metabolism also appeared to occur in most outpatients during the administration of 1 drop daily.

In the house patients, the administration of 1 drop daily caused a maximum reduction in basal metabolism in seven days on the average.

The time that elapsed between the beginning of iodine administration and the onset of a decrease in basal metabolism varied from one to four days. In five of the cases it had started within twenty-four hours after administering only 6 mg. of iodine.

The doses of iodine used at present in the routine preoperative and postoperative treatment for exophthalmic goiter are probably needlessly large. It is doubtful if more than 5 drops of compound solution of iodine daily is ever necessary to produce a maximum effect.

In comparing the effects of various doses of iodine, it is essential to secure a resting level of basal metabolism before medication is begun.

34. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, to be published.

THE DIAZO-COLOR REACTION FOUND IN UREMIA *

I. M. RABINOWITCH, M.D.

MONTREAL, CANADA

In 1925 ¹ there was reported a series of results obtained when the blood of patients with various forms of kidney lesions was tested for the diazo-color reaction by Hewitt's modification ² of Andrewes' original technic. ³ The clinical value of this test was confirmed. Twenty cases in all were observed. It was then found that the reaction was obtained only in cases of severe kidney lesions. In all of the cases in which positive reactions were obtained, the values for blood urea nitrogen were high, ranging between 90 and 210 mg. per hundred cubic centimeters. The creatinine content of the blood specimens was also high. The reaction was not always associated with fatal termination. A patient who had severe nephritis during the course of pregnancy recovered. Nor was there perfect correlation between the degree of retention of urea and the reaction. This was shown in a case of bilateral renal tuberculosis with anuria. The test, then, appeared to be of particular value in differentiating uremia from cerebral arteriosclerosis. As is well known, this differentiation is at times almost impossible to make by the usual clinical methods. The observations may be the same in both conditions; that is, there may be albumin and casts in the urine, hypertension, cardiac hypertrophy, changes in the fundi, headache, muscular twitchings, etc. The best observers often disagree as to whether the signs noted in a given case are due to uremia or to arterial changes in the brain. Since then a number of articles have appeared on the same subject.

Blotner and Fitz ⁴ obtained positive diazo-color reactions in cases with lesser degrees of nonprotein nitrogen retention in the blood than those previously reported. These authors, again, pointed out the prognostic value of the test. They stated that a high blood urea nitrogen test did not have the same prognostic significance when the diazo-color reaction was negative as when it was positive. They also observed that the test was of value in differentiating uremia from other forms of coma.

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* From the Department of Metabolism, the Montreal General Hospital.

1. Rabinowitch, I. M.: *Canad. M. A. J.* **15**:725, 1925.

2. Hewitt, L. F.: *Biochem. J.* **19**:171, 1925.

3. Andrewes, C. H.: *Lancet* **1**:590, 1924.

4. Blotner, H., and Fitz, R.: *Diazo Test in Nephritis*, *J. A. M. A.* **88**:985 (March 26) 1927.

Almost simultaneously, Harrison and Hewitt⁵ and Hunter and Montgomery⁶ reported somewhat similar experiences. Harrison and Hewitt made the additional observation that, on boiling the mixture of protein-free filtrate and the diazo-color reagent, though a yellow brown was always found in the positive case, a similar color may also be obtained with substances other than that responsible for the Andrewes' reaction. Hewitt's modification of Andrewes' procedure, that is, the use of the red color obtained on making the mixture alkaline after heating, eliminates this difficulty. The test thus performed was found positive only in persons with severe kidney damage. Other observations made were: (a) A negative reaction does not exclude uremia, and (b) the degree of urea retention and the diazo-color reaction do not run strictly parallel. The test was somewhat simplified in order to make it of greater clinical application. Hunter and Montgomery also suggested a modification of the test to increase its sensitivity. Both Harrison and Hewitt and Hunter and Montgomery made the observation that the substance responsible for the reaction is a constituent of normal urine. Harrison and Bromfield⁷ have shown that the substance responsible for the reaction is an indoxyl compound, presumably indican, or possibly, in part, indoxyl glycuronate.

Since then, a paper has been published by Rabson and Jacobs,⁸ reporting their experiences with twenty-one cases. These authors showed that four of seven patients whose blood gave positive diazo-color reactions are now living, and their general condition is improved. It was also observed that the test was not positive in all of the cases of coma associated with severe kidney damage, and that it did not always differentiate uremia from the comas of other origin. The conclusion was also made that the creatinine content of blood is of greater value than the diazo test in estimating the extent of kidney damage.

In the laboratory of this hospital the test has been part of the routine in the study of kidney efficiency, since it was first reported, and many hundreds of observations have been made. Clinical and laboratory records have been carefully recorded and correlated. The purpose of this paper is to report further experiences. These demonstrate that, when certain variables are considered in the interpretation of the data, there is no reason to alter the original view expressed as to the prognostic value of this test. In other words, this test differs in no way from all other laboratory procedures, for the proper use of which it is important to correlate laboratory results with clinical signs and symptoms.

5. Harrison, G. A., and Hewitt, L. F.: *Brit. M. J.* **2**:1138 (Dec. 17) 1927.

6. Hunter, G., and Montgomery, R. C.: *Canad. M. A. J.* **17**:1448, 1927.

7. Harrison, G. A., and Bromfield, R. J.: *Biochem. J.* **22**:43, 1928.

8. Rabson, S. M., and Jacobs, L.: Value of Diazo Test on the Blood, *Arch. Int. Med.* **42**:386 (Sept.) 1928.

In view of this experience, I have not found any reason for modifying the procedure described by Hewitt, except that instead of boiling the mixture for thirty seconds as described before making the mixture alkaline, it is allowed to remain in water for about five minutes after the water has been brought to the boiling point and the flame removed. It was frequently noted that heating the test tube directly over the flame led to negative results when the substance responsible for the reaction was actually present. That the temperature of the mixture prior to the addition of alkali is an important factor is also suggested from the recent observations of Harrison,⁹ who found that if the concentration of the substance responsible for the reaction is very small, it is easy to miss the fleeting red tint if the alkali is added to the hot mixture. To overcome this, the mixture, after it has been boiled sufficiently to produce the maximum brown color, is cooled under the tap. The alkali is then added.

It is recognized, clinically, that persons may have severe lesions of the kidney and recover. These include the albuminurias of severe infections, the well recognized acute nephritis with pallor, edema and other changes, mechanical obstructions to the urinary outflow, some surgical lesions of the kidney, anuria of diabetic coma, and other conditions. The blood of such persons may show marked retentions of urea and creatinine and give positive diazo reactions. In such cases, therefore, the diazo-color test differs in no way from the estimation of the urea and creatinine contents of blood. The importance of considering these forms of acute kidney damage in the interpretation of the urea and creatinine contents of blood was emphasized some time ago.¹⁰

In our experience, at least, the diazo-color test has proved to be most reliable, from the point of view of prognosis in chronic nephritis. Persons suffering from such acute lesions of the kidney referred to and whose blood may give positive reactions may, just as stated, recover, but we have yet to observe a person with chronic nephritis who has recovered when the lesion of the kidney has progressed to the point of giving a positive reaction. The longest period observed, between the time the positive reaction was first observed and death, was five months.¹¹ Here, again, must be excluded acute exacerbations which may occur during the disease. The latter should obviously be included among the acute lesions of the kidney. Clinically, it is recognized that persons frequently recover from these acute exacerbations.

9. Harrison, J. A.: Personal communication to the author.

10. Rabinowitch, I. M.: *Canad. M. A. J.* **11**:320, 1921.

11. One patient has now been under observation for more than one year with a positive reaction, but the diagnosis is uncertain. There appears to be a combination of chronic nephritis and a surgical lesion with pyuria.

When an attempt was made to correlate the positive reactions with the urea contents of blood in our large series of cases, no correlation was noted. This is shown in table 1. The positive reactions only are recorded. This observation was to be expected, since the prognosis and degree of retention of blood urea are not related.

In the many hundreds of analyses that have been made, though high blood urea values were found associated with negative diazo-color

TABLE 1.—*Absence of Relationship Between Blood Urea Nitrogen and Diazo-Color Reaction*

Urea Nitrogen, Mg. per 100 Cc. of Blood	Incidence of Positive Diazo- Color Reaction
-21	0
21-30	26
31-40	11
41-50	8
51-60	24
61-70	12
71-80	14
81-90	18
91-100	8
101-110	6
111-120	9
121-130	8
131-140	22
141-150	10
151-160	21
161-170	18
171-180	12
181-190	10
191-200	6
201-	14

TABLE 2.—*Relationship Between Positive Diazo-Color Reaction and Creatinine Content of Blood*

Creatinine, Mg. per 100 Cc. of Blood	Incidence of Positive Diazo- Color Reaction
-1.50	0
1.51-1.75	0
1.76-2.00	0
2.01-2.25	3
2.26-2.50	5
2.51-2.75	5
2.76-3.00	6
3.01-3.25	8
3.26-3.50	7
3.51-3.75	11
3.76-4.00	14
4.01-4.25	16
4.26-4.50	20
4.51-4.75	15
4.76-5.00	23
5.01-	41

reactions, we have yet to find a positive diazo-color reaction associated with a normal blood urea nitrogen. Rabson and Jacobs reported such a case (subject S. F.).

The observations with regard to the relationship between positive reactions and the creatinine content of blood differ from those with regard to urea. Here there appears to be a relationship. The results are shown in table 2. Only positive reactions are, again, recorded.

Here, again, our observations differ from those of Rabson and Jacobs. We have yet to observe a positive diazo-color reaction with a creatinine value of less than 2 mg. per hundred cubic centimeters of blood. With regard to negative reactions, Rabson and Jacobs, in a series of fourteen cases, found four patients whose blood gave such reactions, in spite of creatinine values greater than 5 mg. per hundred cubic centimeters. In our series, only two of forty-three specimens of blood with such creatinine values were met with which gave negative diazo-color reactions.

When consideration is given to the different forms of kidney lesions and to the view previously reported regarding the urea-creatinine relationships,¹² an explanation for the aforementioned observations is suggested. In both of our cases with creatinine values greater than 5 mg. per hundred cubic centimeters of blood and negative diazo-color reactions, the anurias were due to mechanical block (prostatic hypertrophy). Of the four patients in the cases reported by Rabson and Jacobs whose blood gave positive diazo-color reactions and who recovered, three had acute lesions. G. R. had acute suppression of urine following parturition, H. M. had prostatic hypertrophy with urinary retention, and J. C. had urinary retention with acute cholecystitis.

CONCLUSIONS

Our experiences with the diazo-color reaction, therefore, lead to the following conclusions:

1. A positive diazo-color reaction is not found in any condition other than severe kidney damage.

2. A positive reaction may frequently be found in persons with severe kidney damage, and such persons may recover. Such cases include the albuminurias of severe infections, the well recognized form of acute nephritis with pallor, edema, etc., acute exacerbations of chronic nephritis, mechanical obstructions to the urinary outflow, surgical lesion of the kidneys with urinary retention and the anuria of diabetic coma.

3. When acute exacerbations of the disease are excluded, a positive reaction occurring in the course of chronic nephritis has invariably, at least in our experience, meant unfavorable prognosis.

4. When all of the aforementioned factors are given consideration, the test is of value in differentiating uremia from cerebral arteriosclerosis.

12. Patch, F. S., and Rabinowitch, I. M.: Urea and Creatinine Contents of Blood in Renal Disease: Statistical Analysis of 5,000 Observations, *J. A. M. A.* **90**:1092 (April 7) 1928.

BLOOD OF NORMAL YOUNG WOMEN RESIDING IN A SUBTROPICAL CLIMATE

RED CELLS, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, COLOR
INDEX, VOLUME INDEX AND SATURATION INDEX *

M. M. WINTROBE, M.D., PH.D.

NEW ORLEANS

An investigation similar to that previously reported in 100 young men residing in the Southern United States¹ has been carried out on 50 women between the ages of 17 and 30 residing in the same region. This work was undertaken, in the first place, to determine the validity of the hypothesis that an anemia of purely climatic origin is present in otherwise healthy persons residing in tropical and subtropical climates and is the cause of the pallid appearance of many of these persons, and, secondly, in order to furnish further data from which to calculate normal blood standards. In spite of the fundamental importance of accurate knowledge in respect to the number of red cells, the amount of hemoglobin and the volume of packed red cells in the blood of normal healthy persons, it is surprising to find on what poor foundation the accepted standards have been based.

The usually accepted conceptions of the normal blood count in men and women are founded on determinations made in the middle of the nineteenth century on four subjects by Vierordt² and Welcker.³ Since that time the few investigations which have been undertaken have not advanced the knowledge in this field in any manner commensurate with the progress in other fields of medicine. In spite of the common knowledge of the degree of error entailed in the counting of red cells, as well as the wide variation observed in healthy persons, it was only recently that the validity of drawing conclusions on the basis of only a few

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* From the Department of Medicine, Tulane University School of Medicine.

1. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, *Arch. Int. Med.* **43**:96 (Jan.) 1929. Wintrobe, M. M.: Hemoglobin Standards in Normal Men, *Proc. Soc. Exper. Biol. & Med.* **26**:848 (June) 1929.

2. Vierordt, K.: Zählungen der Blutkörperchen des Menschen, *Arch. f. Physiol.* **11**:327, 1852.

3. Welcker, H.: Des Gehalt des Blutes in gefärbte Körperchen, approximativ bestimmt nach bei der methodischer Verdünnung des Blutes entstehenden Färbung, *Arch. d. Ver. f. gemensch. Arb. z. Ford. d. wissensch. Heilkund.*, Göttingen **1**:195, 1854.

observations was questioned and an attempt was made to supply a large series of observations in healthy men⁴ and women.⁵

Likewise, the wide variation in the amount of hemoglobin accepted as the equivalent of 100 per cent by the various hemoglobinometers reflects the inaccurate foundation on which they are based. Finally, the value of information derived from a knowledge of the volume of packed red cells in a given sample of blood, which can be determined more easily and, incidentally, more accurately than either the number of red cells or the amount of hemoglobin, has received little attention and its importance in clinical diagnosis has been practically neglected.

SUBJECTS EXAMINED

The subjects of this examination were normal female students between the ages of 17 and 30. Twelve were medical students and the remainder, students in the general academic courses of Newcomb College. The majority had had a physical examination in the past year, and all felt well at the time of the examination. Many habitually took part in athletics. Practically the entire group was born in the United States, the majority of American-born parents. All have resided in the Southern States (chiefly Louisiana, Mississippi and Alabama) for at least the last three years. The examinations were made during the months of February, March and April, during which time the atmospheric temperature ranged between 50 and 84 F.

No selection was made with reference to the menstrual period. The examinations were conducted whenever the subjects chose to present themselves, whether they were menstruating at the time or not. The time in the menstrual cycle at which the examinations were made, however, was noted. The possible influence of menstruation will be discussed elsewhere.

Most of the specimens of blood were drawn after noon, between 1 and 5 p. m., while a few were drawn earlier in the day.

METHODS

Five cubic centimeters of venous blood was drawn from a vein of the arm into a dry syringe and quickly placed in test tubes containing 10 mg. of finely powdered neutral potassium oxalate with which the blood was thoroughly mixed. Care was taken to keep the tourniquet on the arm for as brief a time as possible in order to avoid any error introduced by congestion of the arm.

4. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch. Int. Med.* **37**:685 (May) 1926.

5. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *Arch. Int. Med.* **39**:643 (May) 1927.

The method of using venous blood for determining red cell counts and hemoglobin instead of capillary blood, as is the custom, requires some consideration. The use of venous blood has the merit that, in normal persons at least, flow in the veins is always active and determinations are more likely to be constant, whereas the influence of stasis, cold and other temporary external factors may be encountered in the capillaries.⁶ Furthermore, unless a free flow of blood is obtained by means of a deep wound, serum and lymph may be squeezed out from the finger or ear instead of a truly representative quantity of red cells. My own investigations show that there is no regular difference between cell counts and hemoglobin determinations made on blood taken from the vein or the finger pulp. The experience of others supports this conclusion.⁷

The addition of oxalate to venous blood in the proportion of 10 mg. to 5 cc. of blood has no influence on red cell count or hemoglobin, although a shrinkage of 3.7 per cent in cell volume is produced.¹

The technic followed in the determination of red cell counts and hemoglobin was the same as in the earlier work on men¹ and need not be again described. For the determination of cell volume a specially made hematocrit was used. This hematocrit is described in detail elsewhere.⁸ It was substituted for the specially calibrated centrifuge tube used in the work on men because less blood is required, and the reading of cell volume is more easily and more accurately made. Complete packing was secured by centrifugation at 3,000 revolutions per minute for thirty minutes. As the heat produced in the centrifuge caused a slight expansion of the blood, readings were not made until the tubes had regained the temperature of the surrounding air. An addition of

6. Drinker, C. K.: *The Pathological Physiology of Blood Cell Formation and Blood Cell Destruction*, Oxford Medicine, vol. 2, pt. 2, p. 509.

7. Yarbrough, N.: *Blood Counts with Oxalated Blood*, J. Lab. & Clin. Med. **7**:172 (Dec.) 1921. Foord, A. G.: *Blood Counts with Oxalated Blood Compared with Ordinary Counts*, J. Lab. & Clin. Med. **8**:343 (Feb.) 1923. DaCosta, J. C.: *Clinical Hematology*, Philadelphia, P. Blakiston's Son & Company, 1907, p. 173. Bürker, K.: *Vergleichende Untersuchungen über den Gehalt des menschlichen Blutes an Hämoglobin und Erythrocyten in verschiedenen Teilen des Gefäßsystems*, Arch. f. d. ges. Physiol. **167**:143 (April) 1917. Bing, H. I.: *On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances*, Acta med. Scandinav. **53**:833, 1921. Hess, Otto: *Vergleichende Untersuchungen am arteriellen, kapillaren und venösen Blut des Menschen*, Deutsches Arch. f. klin. Med. **137**:200 (Aug.) 1921. Duke, W. W., and Stofer, D. D.: *A Comparison of Capillary and Venous Blood in Pernicious Anemia*, Arch. Int. Med. **30**:94 (July) 1922. Rud, E. J.: *Le nombre des globules rouge chez les sujets normaux et leurs variations dans les diverses conditions physiologiques*, Acta med. Scandinav. **57**:142, 1922-1923. Osgood (footnote 4).

8. Wintrobe, M. M.: *A Simple and Accurate Hematocrit*, J. Lab. & Clin. Med. **15**:287 (Dec.) 1929.

3.7 per cent was made to the cell volume determined in each case in order to allow for shrinkage resulting from the addition of oxalate to blood in the proportions mentioned.

ACCURACY OF METHODS EMPLOYED

Red Cell Counts.—As in the earlier work,¹ two separate dilutions of blood were made and the resulting counts were not accepted unless they agreed within 100,000, the average of two such counts being taken as the result. Calculation of the probable error⁹ shows that this method involves an error of less than 1 per cent. However, since it is possible that two closely agreeing counts may be accidental and that two subsequent counts would differ from these first ones, although again agreeing between themselves, the probable error is more accurately determined

TABLE 1.—*Consecutive Counts on a Single Specimen*

Count No.	No. of Cells Counted	d or Variation from Mean	d ²
1.....	518	+11	121
2.....	520	+13	169
3.....	502	— 5	25
4.....	505	— 2	4
5.....	491	—16	256
Mean.....	507		Σ.575

The probable error is $0.67449 \sqrt{\frac{575}{5}} = 7.23$

The percentage of error in terms of the mean is $\frac{7.23}{507} \times 100 = 1.43$ per cent

by calculation on the basis of the results of several consecutive counts on a single sample of blood. In the example given in table 1 five different dilutions and counts were made.

From these and other similar calculations it is concluded that the probable error of the red cell counts carried out by the method described is not greater than 2 per cent.

Hemoglobin.—The amount of hemoglobin was determined by means of a Newcomer hemoglobinometer restandardized on the basis of a series of parallel determinations by the van Slyke method.¹ In considering the probable error of the hemoglobin determinations, it is necessary to consider the error entailed in the actual reading of the Newcomer instrument as well as the probable error of the correction curve. The result of such an analysis is rather disconcerting. While the probable

9. Probable error can be determined from the standard deviation of a series of consecutive determinations on the same sample of blood. The standard deviation (δ) is calculated from the formula $\delta = \sqrt{\frac{\Sigma (d^2)}{N}}$, where $\Sigma (d)^2$ is the sum of the squares of the differences of the individual readings from the mean of those readings, and N is the number of readings. The probable error is 0.67449 δ .

error of the actual reading of the Newcomer instrument is less than 2 per cent and that the van Slyke determinations approximately 1 per cent, the twenty-nine determinations, on which the correction for the hemoglobinometer used is based, showed a rather high degree of scatter about the correction curve. Thus, samples of blood which gave approximately the same readings on the Newcomer instrument showed an appreciable difference in oxygen capacity and corresponding hemoglobin equivalent as determined by the van Slyke method. The probable error of the correction curve, as calculated by measuring the difference between the actual van Slyke determination for each sample of blood and its equivalent on the theoretical correction curve, is 9.2 per cent.

On the basis of these calculations, then, the total possible error of the hemoglobin determinations reported is from 10 to 12 per cent. In these calculations the error has been exaggerated rather than minimized, and it is likely that the actual error is not so great. I feel that the results here reported are certainly comparable in accuracy with the figures reported by others. It is important to realize, however, that even after careful recalibration of one of the more accurate hemoglobinometers, a rather considerable degree of error may be present. The error resulting from the placid acceptance of the manufacturer's statement that 100 per cent is equivalent to a certain number of grams of hemoglobin is, however, much greater. Thus, in the case of the particular Newcomer instrument which I have attempted to recalibrate, a sample of blood reading 70 per cent showed an oxygen capacity (van Slyke) equivalent to 14.61 Gm. The equivalent of 70 per cent by the correction curve developed is 14.1 Gm., while its equivalent on the manufacturer's statement that 100 per cent on the Newcomer hemoglobinometer is equivalent to 16.9 Gm. would be 11.83 Gm.

It is worth noting that the Newcomer method of hemoglobin determination is much more accurate than the methods more commonly used in clinical medicine. The error of these latter methods is from 20 to 30 per cent or even greater. The only redeeming feature of the commonly used methods of hemoglobin determination is that, although they are almost worthless for the determination of the absolute amount of hemoglobin in the blood, some instruments afford moderately accurate relative conceptions.

Cell Volume.—Two hematocrit determinations were made on each specimen of blood and the average of these two was recorded. With reasonable care in technic the determination of cell volume by the hematocrit method is very accurate. Samples frequently check exactly. The example in table 2 has been chosen to illustrate the determination of the probable error because it represents greater rather than less than usual variation.

The actual variation between several samples of the same specimen of blood is thus no greater than 0.5 per cent. It is surprising that a method which is so simple and yet so accurate has received so little use in clinical laboratory diagnosis. This is explained chiefly by the fact that the value of the information which can be derived from the hematocrit has received little emphasis.

THE RED CELL COUNT IN NORMAL WOMEN

Red cell counts made with reasonable accuracy have been reported for 126 women between the ages of 17 and 30:

Bierring ¹⁰ (Sweden)	3 women, averaging 4.24 million
Gram and Norgaard ¹¹ (Denmark)	6 women, averaging 4.59 million
Bie and Möller ¹² (Denmark)	10 women, averaging 4.74 million
Rud ¹³ (Denmark)	8 women, averaging 4.80 million
Haden ¹⁴ (Missouri)	9 women, averaging 4.33 million
Osgood and Haskins ⁵ (Oregon)	100 women, averaging 4.80 million
Total, 136 women, averaging 4.74 million per cubic millimeter.	

TABLE 2.—*Consecutive Hematocrit Determinations on a Single Specimen*

Sample No.	Reading, Ce.	d	d ²
1.....	37.1	-0.3	0.09
2.....	37.3	-0.1	0.01
3.....	37.6	+0.2	0.04
4.....	37.4	0	0
5.....	37.8	+0.4	0.16
6.....	37.5	+0.1	0.01
Mean.....	37.4		0.31
$\delta = \sqrt{\frac{0.31}{6}} = 0.2273$			
P. E. $\delta = 0.67449 \times 0.2273 = 0.1533$			
Probable error in per cent of mean $\frac{0.1533}{37.4} \times 100 = 0.41$ per cent			

Osgood and Haskins⁵ quoted 184 counts made by ten different investigators on women whose age is not given. The average of these counts is 4.83 million.

The average of counts in the fifty normal women examined in New Orleans is 4.93 million. Unlike the counts in men in the South,¹ there

10. Bierring, K.: Svingninger i erythrocyttallet hos normale mennesker, Ugesk. f. Laeger **82**:1445 (Nov.) 18 1920; quoted by Osgood and Haskins (footnote 5).

11. Gram, H. C., and Norgaard, A.: Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, Arch. Int. Med. **31**:164 (Feb.) 1923.

12. Bie, Valdemar; and Möller, Paul: Constitution du sang humain normal, Arch. d. mal. du coeur **15**:177 (April) 1922.

13. Rud (footnote 7, eighth reference).

14. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:765 (May) 1923.

is no significant difference between the results of counts made in this locality and those made elsewhere. The average of erythrocyte counts made on 186 women, from 17 to 30 years of age, in different parts of the world is 4.78 million.

Chart 1 is a histogram showing the frequency distribution of red cell counts in the fifty normal women. The mean (4.93 ± 0.03) and the median (4.94 ± 0.03) are practically equal and both coincide with the peak of the curve. The tendency to a double peak is not significant. The standard deviation is 0.286 ± 0.018 million, and the coefficient of variation 5.8 per cent.¹⁵ Thus the significant variation of the red cell counts was between 5.22 and 4.64 million (actually 76 per cent ranged

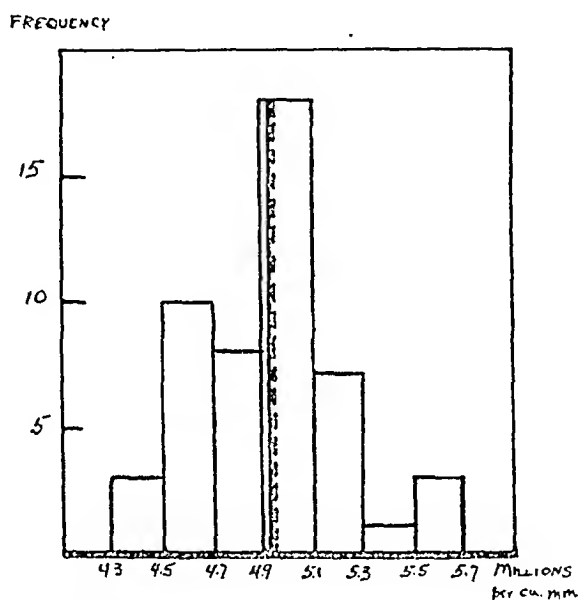


Chart 1.—Histogram showing frequency distribution of variations in red cell counts in fifty young women. The mean is indicated by a straight line, the median by an interrupted line.

between these figures). These results correspond closely to the counts reported by Osgood and Haskins excepting that the latter authors found a larger proportion of counts below 4.5 million.

15. The methods of analyzing the observations here reported are those recommended by Raymond Pearl (*Medical Biometry and Statistics*, Philadelphia, W. B. Saunders Company, 1927, p. 264), and the manner of calculating the various constants is that recommended by this author. The central tendency in a group of observations is measured by the usual arithmetical mean or average, and also by the median. The latter is simply the middle value in a series of observations, 50 per cent of the variates falling above and 50 per cent below it. In a large series of observations, if the distribution of cases is symmetrical, the median will approach closely to the average. The degree of variation is measured by means of the standard deviation and the coefficient of variation. The standard deviation is a constant which has been adopted by biometricians to measure in absolute terms

TABLE 3.—*Observations on the Blood of Fifty Normal Young Women*

Sub- ject	Age	Red Cell Count, Millions per C.Mm.	Hemo- globin, Gm. per 100 Ce.	Hemoglobin, Gm. per 100 Ce. per 5 Million Cells	Color Index	Volume of Cells Ce. per 100 Ce.	Volume of Cells per 100 Ce. per 5 Million Cells	Volume Index	Satura- tion Index
1	32	5.54	14.95	13.50	0.95	39.3	35.6	0.83	1.15
2	28	4.69	12.88	13.72	0.96	37.9	40.5	0.95	1.01
3	18	5.08	13.90	13.69	0.96	38.0	38.3	0.90	1.08
4	20	5.65	15.75	13.95	0.98	41.9	40.6	0.87	1.03
5	17	4.99	14.95	14.09	1.05	38.7	38.8	0.91	1.16
6	21	5.04	13.30	13.20	0.93	38.6	38.3	0.90	1.04
7	18	5.04	15.32	15.21	1.07	39.3	39.0	0.91	1.18
8	24	5.15	14.95	14.51	1.02	42.7	41.4	0.99	1.05
9	20	5.59	15.12	13.52	0.95	41.2	36.0	0.87	1.10
10	20	5.23	14.10	13.49	0.95	39.3	37.6	0.88	1.08
11	19	4.95	14.20	14.39	1.01	41.7	42.1	0.98	1.02
12	20	4.86	13.10	13.49	0.95	37.2	38.3	0.90	1.06
13	19	4.89	13.10	13.40	0.91	36.8	37.6	0.88	1.07
14	20	5.15	13.30	12.90	0.91	40.0	39.7	0.93	0.98
15	19	5.00	13.30	13.30	0.91	36.9	36.9	0.86	1.09
16	20	4.59	12.66	13.57	0.97	39.3	42.8	1.00	0.97
17	20	5.05	14.53	14.40	1.01	41.2	40.8	0.96	1.12
18	20	5.06	13.30	13.18	0.93	40.5	40.0	0.93	0.99
19	18	4.56	12.46	13.89	0.96	37.1	40.7	0.95	1.02
20	23	5.26	15.96	15.18	1.07	43.6	43.0	0.97	1.10
21	20	5.07	14.20	14.00	0.99	41.6	41.0	0.96	1.03
22	21	5.13	14.10	13.74	0.97	39.9	38.9	0.91	1.06
23	18	4.55	11.80	12.98	0.91	36.3	39.9	0.93	0.98
24	19	4.90	13.50	13.79	0.97	40.9	41.8	0.96	1.01
25	19	4.90	12.46	12.70	0.90	40.4	41.2	0.96	0.93
26	21	4.89	13.30	13.60	0.96	40.0	40.9	0.95	1.00
27	20	4.68	13.20	14.10	0.99	37.5	40.1	0.91	1.06
28	22	4.81	14.30	14.88	1.04	38.5	40.0	0.91	1.12
29	23	4.66	13.70	14.70	1.03	38.9	41.7	0.98	1.06
30	22	4.67	13.90	14.89	1.05	39.2	42.0	0.98	1.07
31	21	4.47	12.46	13.91	0.98	36.0	40.2	0.91	0.93
32	21	4.74	14.10	14.90	1.05	39.0	41.2	0.96	1.09
33	20	5.10	14.74	14.94	1.02	41.2	40.4	0.89	1.08
34	22	4.52	12.99	14.38	1.01	35.7	39.5	0.92	1.10
35	30	4.79	13.50	14.10	0.99	38.1	39.8	0.93	1.07
36	18	4.64	12.88	13.88	0.93	38.0	42.0	0.91	1.02
37	17	4.47	12.46	13.91	0.98	36.6	40.9	0.91	1.04
38	25	5.05	12.88	12.71	0.90	39.0	39.5	0.92	0.97
39	28	4.97	14.10	14.19	1.00	38.4	38.6	0.90	1.10
40	22	5.10	15.75	15.45	1.09	42.4	41.5	0.97	1.12
41	31	4.96	14.10	14.20	1.00	40.5	40.8	0.95	1.05
42	19	4.94	13.50	13.69	0.96	41.9	42.4	0.99	0.97
43	31	4.65	13.50	14.50	1.02	39.2	42.4	0.99	1.04
44	20	4.94	13.70	13.99	0.98	40.2	40.7	0.90	1.03
45	19	5.48	15.12	13.80	0.97	44.3	40.4	0.95	1.03
46	20	5.01	14.41	14.39	1.01	42.6	42.5	0.99	1.02
47	19	4.84	14.00	14.48	1.02	40.1	41.5	0.97	1.05
48	23	5.07	11.80	11.62	0.82	35.8	35.2	0.82	0.99
49	24	4.45	13.10	14.71	1.04	37.7	42.3	0.99	1.05
50	27	4.87	13.50	13.84	0.98	38.5	39.5	0.93	1.06
Averages		4.93	13.76	13.97	0.98	39.5	40.3	0.93	1.05

(millions, grams, etc.) the degree of scatter or dispersion of a group of observations. It is a much more accurate index of variation than are maximum and minimum values since the latter are often manifestations of abnormalities or the result of technical error. The coefficient of variation expresses the standard deviation as a percentage of the mean and is thus an expression of the relative dispersion of the variates. The coefficient of variation makes possible the comparison of the variability of any series of observations. Thus in the series here examined the coefficient of variation for red cell counts was 5.8 per cent while that for hemoglobin was 7.2 per cent.

HEMOGLOBIN CONTENT OF THE BLOOD OF NORMAL WOMEN

Hemoglobin determinations made by relatively reliable methods are available for 172 normal women between the ages of 17 and 30. They are as follows:

Williamson ¹⁶ (spectrophotometer)	49 women, averaging 15.11 Gm.
Bie and Möller ¹² (Meisling colorimeter checked by oxygen method)	10 women, averaging 13.30 Gm.
Gram and Norgaard ¹¹ (Autenreith Königsberger colorimeter checked by oxygen method)	6 women, averaging 12.82 Gm.
Rud ¹³ (Autenreith-Königsberger checked by oxygen method)	8 women, averaging 12.28 Gm.
Haden ¹⁴ (van Slyke's method)	9 women, averaging 13.50 Gm.
Osgood and Haskins ⁵ (Osgood-Haskins method)	100 women, averaging 13.69 Gm.
Total, 182 women, averaging 13.95 gm. per hundred cubic centimeters of blood.	

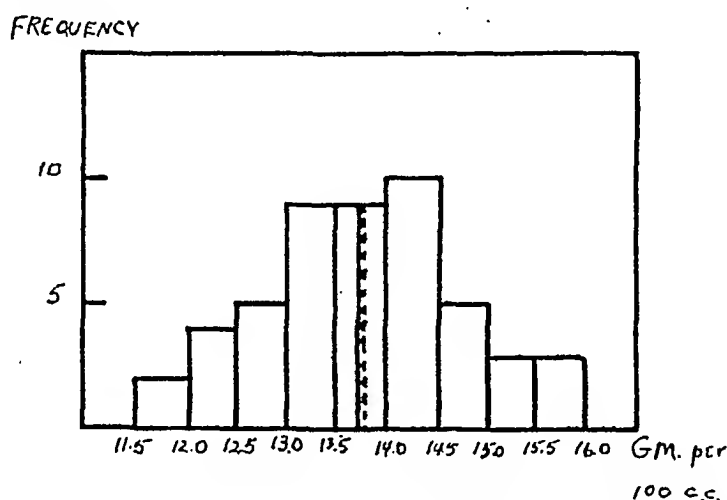


Chart 2.—Histogram showing frequency distribution of variation in hemoglobin in fifty young women.

Osgood and Haskins quoted additional determinations on 133 women whose ages are not given, or in which the methods used were of doubtful accuracy. The average of these is 12.99 Gm.

The average of 13.76 Gm. in the fifty women examined in New Orleans is only slightly lower than the general average and like the red cell counts is not significantly different from observations in other parts of the world. The average of the 232 hemoglobin determinations made on women between the ages of 17 and 30 is 13.91 Gm.

Chart 2 is a histogram showing the frequency distribution of hemoglobin determinations in the fifty women examined. The mean (13.76 ± 0.09) and the median (13.77 ± 0.12) practically coincide. The standard deviation of this series is 0.99 ± 0.07 Gm., and the coefficient of variation 7.2 per cent. The significant variation was thus

16. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

between 12.77 and 14.75 Gm. (Actually 68 per cent ranged between these figures.) This corresponds to Osgood and Haskins' results.

HEMOGLOBIN COEFFICIENT AND COLOR INDEX

The importance of the determination of an accurate standard to serve as the equivalent of 100 per cent hemoglobin has been recently emphasized.¹⁷ Without an accurate standard, color index determinations are valueless. The importance of calculating the standard hemoglobin as the equivalent of 5 million red cells (since this is the number considered to be 100 per cent in the calculation of the color index) has been pointed out by Osgood, and he has introduced the term "hemoglobin coefficient" to represent "the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeters."

Accurate data for the calculation of the hemoglobin coefficient are available for 123 women, from 17 to 30. These are:

Bie and Möller ²²	10 women, averaging 14.0 Gm.
Gram and Norgaard ²¹	6 women, averaging 14.0 Gm.
Rud ²³	8 women, averaging 12.8 Gm.
Haden ²¹	9 women, averaging 15.7 Gm.
Osgood and Haskins ²	100 women, averaging 14.3 Gm.
Total, 133 women, averaging 14.3 Gm.	

The average hemoglobin coefficient for the fifty women here reported is 13.97 ± 0.19 , while the median is 13.94 ± 0.24 Gm. The standard deviation is 0.71 ± 0.05 Gm., and the coefficient of variation 5.1 per cent. The hemoglobin coefficient calculated on the basis of a total of 183 available accurate determinations becomes 14.2 Gm. On the basis of this coefficient recalculation of color indexes from the available accurate material shows the average indexes to be as follows:

Haden (Missouri)	9 women, averaging 1.10
Osgood and Haskins (Oregon).....	100 women, averaging 1.00
Bie and Möller (Denmark).....	10 women, averaging 0.99
Wintrobe (Louisiana)	50 women, averaging 0.98
Gram and Norgaard (Denmark)	6 women, averaging 0.98
Rud (Denmark)	8 women, averaging 0.90
Total, 173 women, averaging 1.	

Chart 3 is a histogram showing the frequency distribution of hemoglobin coefficients and corresponding color indexes in fifty women. The mean and median coincide with the peak.

TOTAL CELL VOLUME

In determining cell volume, it is necessary to take note of the nature of the substance used to prevent clotting of the blood, as well

17. Osgood (footnote 4). Osgood and Haskins (footnote 5).

as the accuracy of the hematocrit employed and the completeness of packing of the cells. Solutions or solid substances added to the blood in order to prevent coagulation alter its isotonicity or dilute it and due allowance must be made for this. It has already been mentioned that oxalate added to blood causes a shrinkage of cell volume.

Determinations of cell volume carried out by accurate methods in normal young women from the ages of 17 to 30 are listed below. An addition of 3.5 per cent has been made to Osgood's average of 41 cc. to allow for shrinkage resulting from the addition of oxalate. No correction was necessary for the figures supplied by the other investigators quoted.

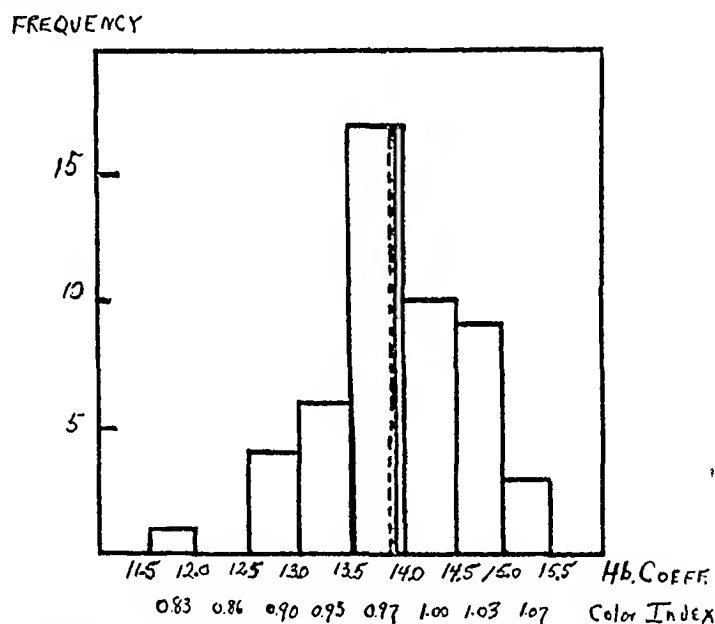


Chart 3.—Histogram showing frequency distribution of variation in hemoglobin coefficients and color indexes in fifty young women.

Gram and Norgaard ¹¹	6 women, averaging 40.4 cc.
Haden ¹⁴	9 women, averaging 39.7 cc.
Gram ¹⁸	12 women, averaging 41.0 cc.
Bie and Möller ¹²	10 women, averaging 38.7 cc.
Osgood and Haskins ⁵	100 women, averaging 42.4 cc.

Total, 150 women, averaging 41.7 cc. of packed red cells per hundred cubic centimeters of blood.

The average cell volume found in the fifty women examined in Louisiana was 39.5 cc. The average of the total of 200 determinations made in different parts of the world is 41.1 cc.

Chart 4 shows the frequency distribution of cell volume determinations in the fifty women examined. The mean (39.5 ± 0.19) and the median (39.3 ± 0.24) are almost identical and coincide with the peak

18. Gram, H. C.: A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, *J. Biol. Chem.* **49**:279 (Dec.) 1921.

of the curve. The standard deviation is 2.03 ± 0.14 cc., and the coefficient of variation 5.2 per cent. Sixty-eight per cent ranged between 37 and 41.5 cc.

VOLUME COEFFICIENT AND VOLUME INDEX

Although introduced by Capps as early as 1903,¹⁹ the importance and value of the calculation of volume index have received little attention. With the prevailing inaccurate methods of hemoglobin estimation, and the comparative simplicity and much greater accuracy of cell volume determination, the calculation of the volume index is of particular value. The information derived is, to a large extent, similar to that derived from the determination of color index while the greater accuracy of the volume index makes it particularly useful. The volume

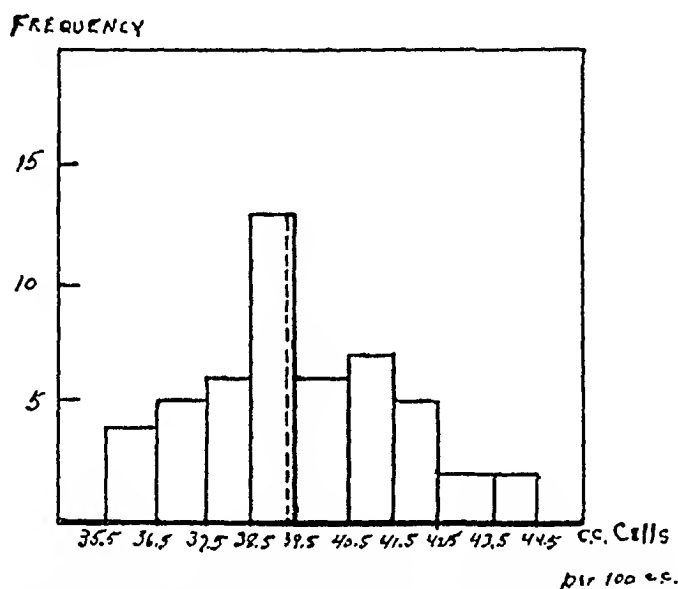


Chart 4.—Histogram showing frequency distribution of variation in cell volume in fifty young women.

index is determined by dividing the cell volume (expressed in per cent of the normal) by twice the number of red cells. As was indicated in regard to hemoglobin, a "volume coefficient" expressing the normal cell volume per five million red cells must be determined to represent 100 per cent. Volume coefficients calculated from data supplied by various authors are as follows:

Gram and Norgaard	6 women, averaging 44.0 cc.
Haden	9 women, averaging 46.2 cc.
Bie and Möller	10 women, averaging 40.8 cc.
Osgood and Haskins	100 women, averaging 44.2 cc.

Total, 125 women, averaging 44.1 cc. of packed red cells per hundred cubic centimeters of blood.

19. Capps, J. A.: A Study of Volume Index, Observations upon the Volume of Erythrocytes in Various Disease Conditions, *J. M. Research* 5:367 (Dec.) 1903.

The average volume coefficient for the fifty women examined is 40.3 ± 0.16 , while the median is 40.4 ± 0.21 . The standard deviation is 1.76 ± 0.12 , and the coefficient of variation is 4.4 per cent. The average volume coefficient, based on the total of 175 women, is 42.9 cc. This coincides closely with the volume coefficient suggested by Osgood and Haskins (42.8).

Accepting this figure of 42.8 cc. as the volume coefficient for normal women from 17 to 30 years of age, recalculation of volume indexes from the available data shows the following:

Haden	9 women, averaging 1.07
Osgood and Haskins	100 women, averaging 1.03
Gram and Norgaard	6 women, averaging 1.02
Bie and Möller	10 women, averaging 0.97
Wintrobe	50 women, averaging 0.93
Total, 175 women, averaging 1.	

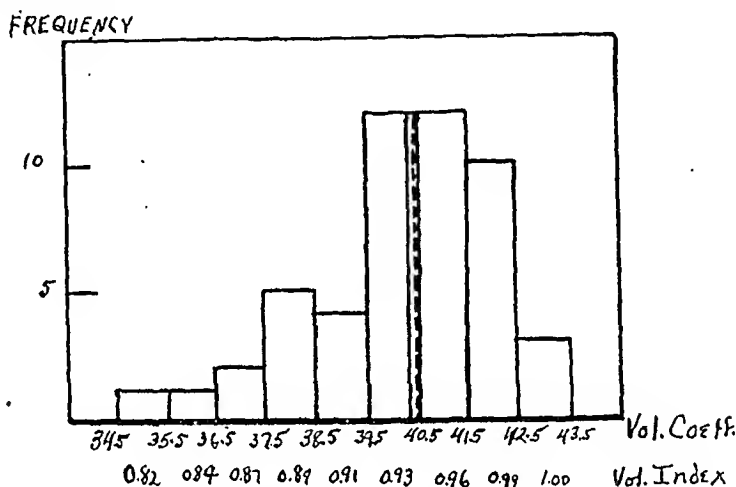


Chart 5.—Histogram showing frequency distribution of variation in volume coefficients and volume indexes in fifty young women.

Chart 5 shows the frequency distribution of volume coefficients and corresponding volume indexes in the fifty women examined. The mean and median coincide with the peak of the curve.

SATURATION INDEX

The saturation index²⁰ expresses the ratio of hemoglobin to the size of the red cells and is calculated by dividing the percentage of hemoglobin by the cell volume percentage. It is a true expression of the saturation of erythrocytes with hemoglobin. Supersaturation of cells with hemoglobin never occurs, according to Haden, and saturation is diminished only in certain types of anemia. In the normal the saturation index is approximately 1.

20. Wintrobe and Miller (footnote 1). Osgood (footnote 4). Osgood and Haskins (footnote 5). Haden (footnote 14).

Chart 6 shows the frequency distribution of saturation indexes of the series of women examined. Calculation of saturation indexes from available, accurate data shows the following:

Wintrobe	50 women, averaging 1.05
Haden	9 women, averaging 1.03
Bie and Möller	10 women, averaging 1.02
Osgood and Haskins	100 women, averaging 0.97
Gram and Norgaard	6 women, averaging 0.96
Total, 175 women, averaging 1.	

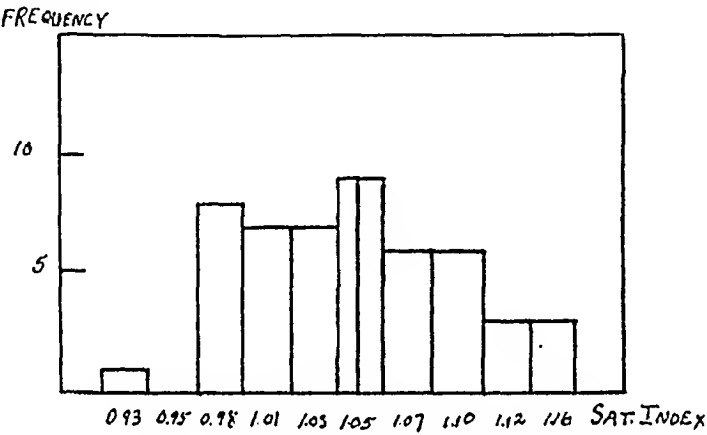


Chart 6.—Histogram showing frequency distribution of variation in saturation indexes in fifty young women.

TABLE 4.—Observations on the Blood of Healthy Young Women from 12 to 30 Years of Age in Different Parts of the World *

Author	Subjects		Red Blood Cells in Millions	Hemoglobin		Cell Volume		Indexes		
	Number	Location		Gm.	Coef- ficient	Cells per 100 Cc.	Coef- ficient	Color	Vol- ume	Satu- ration
Osgood and Haskins ⁵	100	Oregon	4.80	13.69	14.3	42.4	41.2	1.00	1.03	0.97
Wintrobe ¹	50	Louisiana	4.93	13.76	14.0	39.5	40.2	0.93	0.93	1.05
Haden ¹⁴	9	Missouri	4.33	13.50	15.7	39.7	46.2	1.10	1.07	1.03
Bie and Möller ¹²	10	Denmark	4.74	13.30	14.0	38.7	40.8	0.99	0.97	1.02
Gram and Norgaard ¹¹	6	Denmark	4.59	12.82	14.0	40.4	44.0	0.93	1.02	0.93
Rud ¹³	8	Denmark	4.80	12.28	12.8	0.90
Blerring ¹⁰	3	Sweden	4.21
Williamson ¹⁶	49	Illinois	15.11
Gram ¹⁸	25	Denmark	41.0
Averages.....			4.78	13.91	14.2	41.0	42.9	1.00	1.00	1.00

* Calculations are based on a hemoglobin coefficient of 14.2 Gm. and a volume coefficient of 42.8 cc.

TABLE 5.—Summary of Blood Determinations in Young Men and Women Residing in the Southern States

Subjects	Red Blood Cells in Millions	Hemoglobin		Cell Volume	
		Gm.	Coefficient	Cc.	Coefficient
100 Men	5.85	17.00	14.5	46.5	40.0
50 Women	4.93	13.70	14.0	39.5	40.2

SUMMARY AND CONCLUSIONS

1. Blood determinations in fifty healthy young women from the ages of 17 to 30 residing in the southern states have been carried out with the object of investigating the hypothesis that an anemia of purely climatic origin is present in otherwise healthy persons residing in tropical and subtropical climates and is the cause of the pallid appearance of many of these persons, and, secondly, in order to furnish further data from which to calculate normal blood standards.

2. The results of these determinations may be summarized as follows:

(a) The average red cell count was 4,930,000 per cubic millimeter with 76 per cent between 4,640,000 and 5,220,000.

(b) The average amount of hemoglobin was 13.76 Gm. per hundred cubic centimeters of blood with 68 per cent between 12.77 and 14.75 Gm.

(c) The average hemoglobin coefficient was 13.97 Gm.

(d) The average volume of packed red cells was 39.5 cc. per hundred cubic centimeters of blood with 68 per cent between 37 and 41.5 cc.

(e) The average volume coefficient was 40.3 cc.

3. Like the results of blood determinations in men residing in a subtropical climate, these results lend no support to the hypothesis that a physiologic anemia exists in such a climate.

4. The average normal figures for young women from 17 to 30, based on a number of accurate determinations in different parts of the world, are 4,780,000 red cells per cubic millimeter, 13.9 Gm. of hemoglobin and 41.1 cc. of packed red cells per hundred cubic centimeters of blood. The average hemoglobin coefficient is 14.2 Gm., and the average volume coefficient is 42.9 cc.

THE CLINICAL VALUE OF TESTS OF LIVER FUNCTION *

E. F. FOLEY, M.D.

CHICAGO

This study is an effort to evaluate clinically certain so-called tests of liver function on the basis of the results obtained from their use in cases of known or anticipated diseases of the liver. The difficulties encountered in the application of functional tests to the liver have been commented on frequently in recent literature and have been concisely summarized by Carlson.¹ A critical survey of the many liver function tests which have been introduced led Mann and Bollman² to the conclusion that the tests which offered the greatest clinical possibilities were those concerned with the measurement of serum bilirubin and the excretion of specific dyes. These observations have been supported in general by the workers who have applied the tests to clinical material, the van den Bergh reaction and the icterus index being used in the study of serum bilirubin and one of the halogenated phenolphthaleins as the specific dye.

These tests deal with functions which are entirely excretory in nature: in one instance, the excretion of a product which is normally eliminated by the liver, and in the other instance, a foreign substance (dye) which happens to be specifically removed by the liver. Since the biliary passages are an indispensable part of the excretory unit of the liver, Murphy³ suggested that these tests be considered as biliary function tests.

The clinical use of the van den Bergh reaction and the icterus index has led to the establishment of a normal range of serum bilirubin which varies within somewhat narrow limits according to the results obtained by various workers. Thus the van den Bergh test,⁴ with the diazo reagent, gave from 0.1 to 0.25 mg. per hundred cubic centimeters of blood as the

* Submitted for publication, Oct. 27, 1928.

* From the Department of Medicine, Research and Educational Hospital, University of Illinois.

1. Carlson, A. J.: *Physiology of Liver: Present Status of Our Knowledge* J. A. M. A. **85**:1468 (Nov. 7) 1925.

2. Mann, F. C., and Bollman, J. L.: *Liver Function Tests*, Arch. Path. & Lab. Med. **1**:681 (May) 1926.

3. Murphy, W. P.: *Boston M. & S. J.* **194**:297, 1926; *Biliary System Function Tests*, Arch. Int. Med. **37**:797 (June) 1926.

4. Van den Bergh, A. A. Hijmans: *Presse méd.* **29**:441, 1921.

average values obtained in normal persons; Andrewes,⁵ Lepelne,⁶ McNee,⁷ Ravdin,⁸ Hall,⁹ Hazelhorst¹⁰ and Steen¹¹ agreed substantially with these figures. Schiff¹² found that in the majority of his cases there was 0.8 mg. per hundred cubic centimeters or less and considered 1 mg. as the upper limit, allowing 0.2 mg. for fluctuation during the day. Greene and his co-workers¹³ set 2 mg. per cent as the upper limit of normal, thus including cases of physiologic hyperbilirubinemia. In 35 per cent of the normal serums examined by Feigl and Querner,¹⁴ no measurable color change occurred. Since the color standard represents the color developed by a bilirubin concentration of 1:200,000 or 0.2 mg. per cent, these serums contain less than 0.2 mg. per cent. Similar results were obtained by Hazelhorst¹⁰ in 33 per cent of his cases, by Schiff¹² in 34 per cent and by Steen¹¹ in 82 per cent. That the direct reaction occurs in cases of frank obstructive jaundice and the indirect in normal cases and in cases of hemolytic jaundice is fairly well conceded though the differential diagnostic value is not so generally accepted. Thus Greene and his co-workers¹³ used the indirect reaction merely as a means of developing the measurable color for the quantitative estimation of serum bilirubin.

With the icterus index, the normal values have been more definitely established. Meulengracht,¹⁵ and later Bernheim,¹⁶ found the majority of normal values to range from 3 to 5, while hyperbilirubinemia, insufficient to produce clinical icterus, gave results from 6 to 16 and frank jaundice above 30. Later, Bernheim¹⁷ showed that cases of severe secondary anemia were associated with hypobilirubinemia with values of less than 3. Objections have been raised to the icterus index because slight changes of the color of the serum may result from other

5. Andrewes, C. H.: *Quart. J. Med.* **18**:19 (Oct.) 1924.

6. Lepelne, G.: *Deutsches Arch. f. klin. Med.* **132**:96, 1926.

7. McNee, J. W.: *Brit. M. J.* **1**:716, 1922.

8. Ravdin, E. G.: *Am. J. M. Sc.* **169**:850, 1925.

9. Hall, W. W.: *U. S. Nav. M. Bull.* **24**:843, 1926.

10. Hazelhorst: *J. Lab. & Clin. Med.* **12**:529, 1927.

11. Steen, R. E.: *Irish J. M. Sc.*, 1927, p. 573.

12. Schiff, L.: *Serum Bilirubin in Health and in Disease*, *Arch. Int. Med.* **40**:800 (Dec.) 1927.

13. Greene, C. H.; Snell, A. M., and Walters, W.: *Diseases of the Liver: Survey of Tests for Hepatic Function*, *Arch. Int. Med.* **36**:248 (Aug.) 1925.

14. Feigl, J., and Querner, E.: *Ztschr. f. d. ges. exper. Med.* **9**:153, 1919.

15. Meulengracht, E.: *Bilirubin Colorimeter*, *Deutsches Arch. f. klin. Med.* **137**:38, 1921; *Abstr. J. A. M. A.* **77**:1141 (Oct. 1) 1921.

16. Bernheim, A. R.: *Icterus Index (A Quantitative Estimation of Bilirubinemia): Aid in Diagnosis and Prognosis*, *J. A. M. A.* **82**:291 (Jan. 26) 1924.

17. Bernheim, A. R.: *Significance of Variations of Bilirubinemia*, *Arch. Path. & Lab. Med.* **1**:747 (May) 1926.

pigments than bilirubin, notably carotin and luetin and to the difficulty occasionally encountered in matching the pale yellow of the lower dilutions.

PROCEDURE

Thirty minutes after the intravenous injection of the required amount of bromsulphalein (2 mg. per kilogram of body weight) about 10 cc. of blood was drawn, special care being taken to avoid even a trace of hemolysis. After allowing the sample to clot and after centrifugation, the serum was pipeted off and divided into three small tubes. One of these was compared directly with the proper permanent standard of potassium dichromate prepared according to the method recommended by Murphy³ for the icterus index. The second was alkalinized with 10 per cent sodium hydroxide to develop the color of the dye. This was then matched with the standards of the dye, the sample which had previously served for the icterus index being used as the control. The third specimen was used for the van den Bergh test which was performed according to the modification of Thannhauser and Anderson.¹⁸ The presence of the unalkalinized dye did not interfere with the reaction.

One hundred patients used as controls were selected from the outpatient department of the Research and Educational Hospital; they were apparently free from gross pathologic changes of the liver. Particular attention was taken to exclude cases in which a history of alcoholism or syphilis was obtained. No attempt was made to group the values for serum bilirubin according to age, since Perkin¹⁹ found no appreciable variation. In the control cases the diazo reaction was of the indirect type, and in thirty-eight cases the color developed was so faint as to be unmeasurable as compared with the standard, and hence contained less than 0.2 mg. per cent. The maximum value obtained in these cases was 1.8 mg. per cent in a medical student who for years was repeatedly told that he "looked yellow." Careful investigation failed to reveal any pathologic changes in either the liver or the hematopoietic system to account for the hyperbilirubinemia, and he was considered to have a case of physiologic hyperbilirubinemia similar to that reported by Gilbert and Lereboullet,²⁰ van den Bergh,⁴ Schiff,¹² Snell and others. In the majority of the cases (71 per cent) the values were less than 0.3 mg. per cent, and in 95 per cent they were less than

18. Thannhauser, J. S., and Anderson, E.: *Deutsches Arch. f. klin. Med.* **137**:179, 1921.

19. Perkin, F. S.: *Blood Bilirubin: Estimation and Clinical Significance*, *Arch. Int. Med.* **40**:195 (Aug.) 1927.

20. Gilbert, A., and Lereboullet, P.: *Comp. rend. Soc. de biol.* **58**:937, 1905; quoted by van den Bergh: *Presse méd.* **29**:44, 1921; quoted by Schiff: *Arch. Int. Med.* **40**:800 (Dec.) 1927.

0.5 mg. per cent. The maximum reading, excluding the case of physiologic hyperbilirubinemia mentioned, was 0.78 mg. per cent.

The icterus index in 99 per cent of the cases was 6 or less, and in three cases it was 2. In the cases of physiologic hyperbilirubinemia, the reading was 8. The average reading in 100 cases was 4.02. The dye used was bromsulphalein, which was introduced by Rosenthal and

TABLE 1.—*Cardiac Failure with Passive Congestion of the Liver*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Hemo- globin	Red Blood Cells	Icterus Index	Direct Van den Bergh Test	Serum Bili- rubin	Dye, per Cent	Clinical Type
1.....	Slight	3	Trace	65	4,200	29	+	2.9	20	Rheumatic
2.....	Soft palate	6	0	80	400	18	+	2.5	20	Rheumatic
3.....	Soft palate	3	0	70	4,200	11	+D	2.1	15	Rheumatic
4.....	Soft palate	4	Trace	75	3,610	16	+D	2.1	20	Rheumatic
5.....	Soft palate	3	0	75	4,400	12	+	1.8	15	Rheumatic
6.....	Soft palate	5	0	83	4,900	10	+	1.8	15	Rheumatic
7.....	Soft palate	3	0	85	4,600	10	+	1.8	15	Rheumatic
8.....	0	4	0	78	3,800	8	0	1.3	10	Rheumatic
9.....	0	3	0	80	4,100	8	0	1.1	5	Rheumatic
10.....	0	2	0	75	3,750	5	0	0.9	5	Rheumatic
11.....	0	3	0	60	3,700	6	0	0.8	10	Rheumatic
12.....	0	3	0	90	4,310	6	0	0.8	5	Rheumatic
13.....	0	2	0	72	4,100	7	0	0.6	5	Rheumatic
14.....	0	3	0	83	4,300	5	0	0.6	10	Rheumatic
15.....	0	3	0	60	2,650	5	0	0.5	10	Rheumatic
16.....	Slight	2	Trace	72	3,650	18	+	2.6	25	Syphilitic
17.....	Soft palate	2	0	90	4,950	8	+	1.8	10	Syphilitic
18.....	Soft palate	2	0	65	4,756	12	+	1.6	15	Syphilitic
19.....	0	2	0	65	3,100	6	0	0.8	15	Syphilitic
20.....	0	1	0	70	3,850	6	0	0.8	10	Syphilitic
21.....	0	2	0	90	4,100	6	0	0.61	15	Syphilitic
22.....	0	2	0	90	5,800	8	0	0.6	10	Syphilitic
23.....	0	3	0	80	3,900	7	0	0.52	10	Syphilitic
24.....	0	2	0	65	4,150	5	0	0.5	5	Syphilitic
25.....	0	2	0	71	4,100	6	0	0.4	10	Syphilitic
26.....	0	3	0	75	4,610	13	0	0.9	20	Myocardial nephritis
27.....	0	3	0	77	5,100	11	0	0.8	15	Myocardial nephritis
28.....	++	3	+	79	3,800	83	+	8.7	40	Rheumatic alcoholism
29.....	+	3	+	80	4,100	56	+	5.1	30	Rheumatic alcoholism
30.....	+	3	+	60	2,100	24	+D	3.9	25	Myocardial cirrhosis
After compen- sation.....	0	3	0	10	0	1.8	20	

White. None of the reactions which condemned the use of phenol-tetrachlorophthalein was noted in any of the cases. In the control cases no dye was retained in the serum thirty minutes after injection.

CARDIAC FAILURE WITH PASSIVE CONGESTION OF THE LIVER

There were thirty patients in the groups with cardiac failure who presented the typical picture of broken compensation with tender enlargement of the liver. Seventeen of these cases were on a rheumatic basis, two patients had aortic as well as mitral involvement, two gave

a history of drinking heavily just prior to the onset of symptoms and were jaundiced, and one had evidence of a cirrhosis following the establishment of compensation. Ten were syphilitic: one of these was jaundiced and had, as found at postmortem examination, a primary aortitis (Rappaport²¹), and two had a myocardial condition on the basis of a chronic nephritis.

Of the rheumatic cases, except the alcoholic, eight terminated fatally, five of which gave direct reactions, two being delayed, with serum bilirubin values from 1.8 to 2.9 mg. The patient with the highest reading was found clinically to be slightly jaundiced; six had definite discoloration of the soft palate. The icterus index reading in these cases was from 10 to 29, showing a decided increase over normal. The development of jaundice as an unfavorable prognostic sign in cardiac

TABLE 2.—*Portal Cirrhosis with Ascites*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh Test, Mg. per Cent	Serum Bilirubin, per Cent	Dye, per Cent
607	0	0	Negative	40	2.100	5	Negative	0.5	10
002	0	0	Negative	51	2.800	7	Negative	0.6	15
2859	0	Palpable	Negative	45	2.200	9	Negative	1.1	25
4828	0	3	Negative	48	3.100	8	+	1.8	15
103	0	2	Negative	55	3.000	5	Negative	0.8	15
4198	0	0	Negative	51	3.040	12	Negative	0.9	25
1108	0	0	Negative	75	3.150	9	Negative	1.4	20
1429	0	1	Negative	70	3.250	7.5	Negative	0.4	5
0008	0	0	Negative	65	2.900	6	Negative	0.9	25
1008	0	0	Negative	60	3.100	8	+	1.2	30
G. E.	0	0	Negative	50	2.100	6	Negative	0.4	15
C. C.	0	?	?	55	3.160	7	Negative	0.6	20
F.	0	Palpable	Negative	65	3.180	9	Negative	1.5	10
A. P.	0	0	0	70	3.650	8	Negative	0.9	10

decompensation has long been recognized clinically. The other fatal case had the lowest reading, 0.5 mg. per cent; the patient, however, had involvement of both the mitral and the aortic orifices and ran the typical course of a recurrent endocarditis.

In the syphilitic cases, direct reactions with readings of from 1.6 to 2.6 mg. per cent and icterus indexes of from 8 to 18 were obtained in three cases which terminated in death. In the other cases the readings of from 0.4 to 0.8 mg. and indexes of from 5 to 8 had a tendency to be on a lower level than those obtained in mitral lesions. The tendency of the higher readings to be more common in the mitral lesions has been commented on by Fishberg,²² Meulengracht²³ and Schiff.¹² In one of the two alcoholic patients with cardiac decompensation, the

21. Rappaport, B. Z.: Primary Acute Aortitis, *Arch. Path. & Lab. Med.* **2**:653 (Nov.) 1926.

22. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, *J. A. M. A.* **80**:1516 (May 26) 1923.

23. Meulengracht, E.: *Deutsches Arch. f. klin. Med.* **132**:285, 1920.

cardiac breakdown was definitely attributed to the exposure resulting from recent and frequent intoxication. In these cases a prompt direct reaction was obtained with relatively high readings. The recovery of these patients would indicate that the jaundice was not a direct result of the cardiac failure. Concomitant jaundice offers no such serious prognosis as does jaundice resulting directly from cardiac failure.

In the cases of cardiac failure with secondarily contracted kidneys, the icterus indexes have a tendency to be higher than the figures for serum bilirubin obtained with the diazo reagent; this can probably be

TABLE 3.—*Carcinoma*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh Test	Serum Bilirubin, Mg. per Cent	Dye, per Cent	Postmortem Diagnosis	
1147	(1)	4	3; mass in right upper quadrant	+	40	3.160	63	+	27.7	15	Adenocarcinoma of gall-bladder
6655	(2)	1	1	+	65	3.800	46	+	6.9	40	
6655	(2)	4	2	+	50	3.100	115	+	22.9	65	
6655	(2)	4	2	+	50	2.900	164	+	35.4	80	Carcinoma of head of pancreas
094	(3)	4	3; mass in right upper quadrant	+	30	2.800	110	+	26.3	65	Carcinoma of pancreas
5586	(5)	0	1	0	60	3.200	4	0	0.6	0	Carcinoma of stomach; metastases to liver
1635	(6)	0	1	0	50	3.000	3	0	0.3	0	Carcinoma of stomach; metastases to liver
1700	(7)	0	Not palpable	0	20	2.000	5	0	0.8	0	Carcinoma of stomach; metastasis to liver
1783	(10)	0	Not palpable	0	71	3.730	3	0	0.6	0	Carcinoma of esophagus
3450	(11)	0	Not palpable	0	55	3.100	3	0	0.2	0	Carcinoma of sigmoid
5533	(8)	0	Not palpable	0	35	3.000	3	0	0.2	0	Carcinoma of ovary and metastasis to liver
P	(12)	0	2	0	40	2.800	8	0	0.5	5	Retroperitoneal sarcoma
1612	(9)	0	0	0	45	3.000	4	0	0.3	0	Lymphosarcoma; metastases to liver
8494	(13)	0	0	0	75	4.101	6	0	0.4	0	Hypernephroma
	(14)	0	0	0	70	4.030	7	0	0.5	0	Carcinoma of prostate
	(4)	4	4	+	71	3.510	116	+	17.6	55	Carcinoma of head of pancreas

explained on the basis of the retention of some pigment other than bilirubin in the serum which is usually excreted through the kidneys. In all cases of cardiac failure the dye test indicated a definite retention varying from 5 to 25 per cent. The exact aid which these tests offer to the clinician in cases of cardiac decompensation seemed to be prognostic. In those cases in which the clinical symptom of jaundice occurs, no laboratory test is necessary to confirm this fact, but in the borderline cases of clinical jaundice, in which it is not possible to decide clinically whether the skin of the patient is icteric or merely sallow, estimation of serum bilirubin is of definite value. The dye test in itself merely indicates a moderately severe dysfunction of the liver, but to it can be attributed no particular diagnostic or prognostic aid in cases of cardiac failure.

In ten cases of catarrhal jaundice, prompt direct reactions were obtained with high values of serum bilirubin and marked retention of dye. The retention of dye seems to parallel to a certain extent the serum bilirubin, as noted by Greene and his co-workers¹³ in experimentally produced obstructive jaundice. Rosenthal and White²⁴ showed that the retention of dye in experimental animals bore a direct relationship to the amount of liver tissue removed. In one of these cases the retention amounted to 90 per cent. While this degree of retention, together with the severe hyperbilirubinemia, indicates a diffuse lesion, it serves to show that all functions are not equally affected. The vital metabolic functions are apparently spared, for even though the liver possesses a factor of safety amounting to 75 per cent, with severe

TABLE 4.—*Disease of the Gallbladder*

Case	Diagnosis	Diagnosis Made by	Jaundice	Bile in Urine	Icterus Index	Direct Van den Berg's Test	Serum Bilirubin, Mg. per Cent	Dye, per Cent
5514	Chronic cholecystitis; fibrosis	Operation	0	0	12	+	1.4	0
7937	Chronic cholecystitis	Operation	±	0	17	+	1.9	0
2137	Subacute and chronic cholecystitis	Operation	0	0	12	+	1.4	0
61656	Subacute and chronic cholecystitis	Operation	0	0	11	0	1.1	0
2252	Stone obstructing common duct	Clinical course and operation	4	+	60	+	15.8	20
3821	Cholecystitis with stone	Graham Cole	0	0	7	0	1.0	0
3148	Cholecystitis with stone	Graham Cole	0	0	8	0	0.4	0
2137	Cholecystitis with stone	Graham Cole	0	0	6	0	0.4	0
6030	Cholecystitis with stone	Graham Cole	0	0	4	0	0.3	0
6214	Cholecystitis with stone	Graham Cole	0	0	3	0	0.2	0

impairment of one function, it would be expected that the patient would be more sick than he is with catarrhal jaundice if all functions were similarly disturbed. Frequent repetitions of the serum bilirubin estimation shows definite changes in the icteric index not apparent in the skin. The injection of bromsulphalein does not increase the serum bilirubin in catarrhal jaundice, indicating that this dye does not offer any further insult to the already injured liver.

Similar results were obtained in cases of "arsphenamine jaundice," with the exception that higher values were more common. There were five patients with severe jaundice, graded 4, clinically. In all a direct positive reaction was obtained with values for serum bilirubin from 16.3 to 35 mg. per cent. The icterus index similarly showed high values, from 95 to 195. The retention of dye seems to parallel to a certain degree the retention of bilirubin. In this connection, patients

24. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test of Hepatic Function, *J. A. M. A.* 84:1112 (April 11) 1925.

under antisyphilitic treatment in the Dermatological Dispensary of the Research and Educational Hospital who are suspected of having disease of the liver are followed up at regular intervals. Gerrard²⁵ noted that the administration of arsphenamine is frequently associated with evidence of latent icterus or hyperbilirubinemia. Three such cases which have been followed up for three, six and nine months, respectively, are included. While none of these patients had the severe clinical picture of intense jaundice seen in the other cases, it is interesting to note the duration of hyperbilirubinemia. It is possible that these patients may later develop a type of cirrhosis. In this field the tests of

TABLE 5.—*Results in Pernicious Anemia Before and After Diet*

Number	Date	Hemo- globin	Red Blood Cells	Icterus Index	Direct Van den Bergh	Indirect Van den Bergh	Dye
9834	May 19, 1928.....	21	0.680	14.0	0	1.8	0
	June 28, 1928.....	54	3.610	4.1	0	0.5	0
9838	May 11, 1928.....	38	1.070	8.0	0	0.61	0
	June 28, 1928.....	49	2.430	7.8	0	0.45	0
9833	May 19, 1928.....	26	1.330	10.0	0	0.9	0
	June 21, 1928.....	46	3.200	4.6	0	0.38	0

TABLE 6.—*Hemolytic Icterus*

Number	Jaun- dice	Liver Edge, Cm.	Spleen	Hemo- globin	Red Blood Cells in Millions	Icterus Index	In- creased Fra- gility	Direct Van den Bergh	Serum Bili- rubin, Mg. per Cent	Dye Test
1.....	±	2	6 cm.	45	3.30	24.0	+	0	2.9	0
After operation...	0	2	650 Gm.	75	3.60	6.0	—	0	0.5	0
2.....	+	2	7 cm.	58	3.62	32.0	+	0	3.8	0
After operation...	0	2	750 Gm.	80	3.90	5.0	—	0	0.45	0
3.....	+	2	4	50	3.10	16.0	+	0	2.1	0
4.....	0	4	6	64	3.95	17.5	+	0	2.6	0

function, particularly the estimation of bilirubin, are highly commended, for they readily detect the presence of one of the absolute contraindications for the administration of the arsenicals.

A few cases of severe fatty liver with jaundice resulting from alcohol are included at this time. The results obtained here are similar to those obtained in the arsenical group. In all there was the history of heavy drinking, inability to eat and sleep and finally the development of visual hallucinations. In addition to the jaundice and the extreme restlessness, examination revealed a large soft liver with a definitely rounded edge. A series of similar cases was reported by LeCount and Singer,²⁶ in which they ascribed the cause of death to a failure of the glycogenic function of the liver.

25. Gerrard, W. I.: Brit. M. J. 1:224, 1924.

26. LeCount, E. R., and Singer, H. A.: Fat Replacement of Glycogen in the Liver as a Cause of Death, Arch. Path. & Lab. Med. 1:84 (Jan.) 1926.

PORTAL CIRRHOSIS WITH ASCITES

In this group there were fourteen cases presenting the clinical picture of advanced cirrhosis with marked ascites requiring paracentesis at frequent intervals. In five the liver was enlarged, and in eight it was not palpable. In five, serum bilirubin values of 1 + mg. per cent were obtained; in nine, there was less than 1 mg. per cent—normal or high normal values. In twelve, the icterus index was in the zone of latent icterus. In all, however, there was definite retention of dye varying from a minimum of 5 per cent to a maximum of 25 per cent. The gross pathologic picture of this type of liver would lead one to expect marked impairment in function. That this does not occur has been explained

TABLE 7.—*Arsphenamine Jaundice*

	Jaundice	Liver Edge	Bile	Icterus Index	Direct	Serum Bilirubin, Mg. per Cent	Dye
1.....	4	8	+	105	+	35.9	85
2.....	4	6	+	175	+	35.1	90
3.....	4	3	+	125	+	25.4	85
4.....	4	4	+	116.3	+	19.2	70
5.....	4	4	+	95	+	16.3	45
6.....	±	1	+	34	Delayed +	4.2	15
10 days.....	—	1 cm.	0	15	Delayed	2.1	5
1 month.....	—	1	0	12	Delayed	1.9	5
6 months.....	—	1	0	12	Delayed	1.8	Trace
9 months.....	—	1	0	8	0	1.6	0
7.....	±	1 cm. on deep inspiration	0	18	Delayed	2.6	5
1 month.....	—	1 cm. on deep inspiration	0	12	Delayed	2.1	5
2 months.....	—	1 cm. on deep inspiration	0	9	0	1.5	5
3 months.....	—	1 cm. on deep inspiration	0	7	0	1.1	Trace
8.....	±	Palpable	0	21	±	2.4	10
6 weeks.....	—	Palpable	0	14	Delayed	1.5	5
3 months.....	—	Palpable	0	9	Delayed	0.9	5
6 months.....	—	Palpable	0	6	0	0.5	0

by Greene and his associates²⁷ by the chronicity of the process which allows time for regenerative changes to occur. There is a definite disproportion between the results obtained with the dye test and those with the measurement of serum bilirubin. The higher values obtained with the dye test would suggest that the regenerative changes which occur compensate to a greater extent for the normal function of the excretion of bilirubin than for the artificial function of the excretion of dyes.

CARCINOMA INVOLVING THE LIVER

Only those cases of carcinoma are included in which postmortem examination or operation definitely proved involvement of the liver. Four of the fourteen cases were associated with jaundice which, as

27. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: Diseases of the Liver: Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. 40:159 (Aug.) 1927.

indicated by the van den Bergh test was of the obstructive type. In these cases high icterus indexes were obtained, as well as marked retention of dye. In six cases of secondary carcinoma of the liver, the dye test was negative, and in only one of these, was there an increase of serum bilirubin. The usual secondary anemia was present in all cases which, according to Bernheim,¹⁷ is associated with hypobilirubinemia. In one case, that of a man who because of jaundice was referred from the department of syphilology where he had presented himself for antisyphilitic treatment, repeated examination showed a high grade progressive type of obstructive jaundice. Post-mortem examination revealed a carcinoma of the head of the pancreas with biliary obstruction. Positive results indicate the presence of metas-

TABLE 8.—*Catarrhal Jaundice*

Number	Jaundice	Liver Edge, Cm.	Bile in Urine	Icterus Index	Van den Bergh Direct	Serum Bilirubin	Dye
1.....	4	8	+	125	+	22.6	90
10 days later....	3	5	+	90	+	17.2	65
2.....	4	7	+	110	+	19.2	70
5 days later....	4	7	+	85	+	16.2	50
3.....	4	7	+	96	+	20.6	55
5 days later....	3	5	+	90	+	18.2	40
4.....	4	6	+	91	+	17.4	65
5.....	4	6	+	90	+	19.2	60
Next day.....	4	6	+	90	+	20.1	60
Next day.....	4	6	+	88	+	20.1	60
Next day.....	4	6	+	83	+	19.4	60
1 week later....	4	6	+	76	+	15.1	50
6.....	4	4	+	68	+	12.0	55
7.....	4	2	+	55	+	11.1	50
8.....	4	2	+	46	+	7.1	50
9.....	4	5	+	45	+	4.2	35
10.....	4	0	+	30	+	3.8	35
11.....	4	3	+	23	+	3.5	25

tases to the liver, but negative results are not conclusive evidence of their absence.

Diseases of the gallbladder present the greatest field for the clinical application of these tests, for in the diagnosis of painful conditions of the upper part of the abdomen, the presence or absence of even a slight degree of jaundice bears great weight. By means of these tests it is possible to show the presence of hyperbilirubinemia before icterus is present clinically. In these ten cases, the diagnosis was confirmed in five by operation and in five by the Graham Cole method of cholecystography. Two of these patients were icteric; four gave a direct positive reaction; six showed hyperbilirubinemia, while four gave normal values for serum bilirubin. In only one was the dye test positive. In seven increased values were obtained with the icterus index. The failures occurred in cases in which the diagnosis of stone in the gallbladder was made by cholecystography, and in which there was apparently no obstruction to the biliary excretion.

The presence of latent icterus as determined by the measurement of the serum bilirubin is a practical help in cases in which disease of the gallbladder is suspected. In chronic disease of the gallbladder, however, whether due to cholelithiasis or to a chronic inflammatory condition, there may be periods in which latent icterus is not present. At such times the bilirubin tests offer no diagnostic help. Bernheim¹⁷ found that there is a latent icterus in cases of duodenal ulcer. This observation reduces the value of these tests in the diagnosis of pain in the upper part of the abdomen.

TABLE 9.—*Fatty Liver (Alcoholic)*

Number	Jaundice	Liver Edge, Cm.	Hemoglobin	Red Blood Cells in Millions	Icterus Index	Direct Van den Bergh	Serum Bilirubin	Dye
1	4	7	80	3.600	118	+	10.1	75
2	4	8	75	4.100	76	+	8.1	80
3	3	7	75	3.500	80	+	6.5	80
4	2	6	85	3.800	60	+	4.8	65

TABLE 10.—*Diseases of the Blood*

Number	Hemoglobin	Red Blood Cells	Icterus Index	Van den Bergh Direct	Serum Bilirubin	Dye	Diagnosis
7743	23	0.999	16	0	2.2	0	Pernicious anemia
1083	38	1.68	15	0	2.2	0	Pernicious anemia
3731	37	1.45	12	0	1.8	0	Pernicious anemia
	24	0.680	14	0	1.8	0	Pernicious anemia
736	30	1.25	13	0	1.6	0	Pernicious anemia
2073	25	1.01	12	0	1.4	0	Pernicious anemia
7615	30	1.20	11	0	1.1	0	Pernicious anemia
4305	38	1.80	10	0	0.9	0	Pernicious anemia
	26	1.330	10	0	0.9	0	Pernicious anemia
2084	36	1.72	8	0	0.9	0	Pernicious anemia
1140	55	2.16	8	0	0.8	0	Pernicious anemia
6319	39	1.80	6	0	0.6	0	Pernicious anemia
2161	50	3.32	3	0	0.3	0	Myeloid leukemia
3923	55	3.75	3	0	0.2	0	Myeloid leukemia
1537	40	3.55	2	0	0.2	0	Myeloid leukemia
5209	35	2.10	1	0	0.2	0	Myeloid leukemia
2140	140	7.20	4	0	0.4	0	Polycythemia vera
1568	120	6.50	6	0	0.4	0	Polycythemia vera

In twelve cases of pernicious anemia, ten showed latent icterus with readings from 8 to 18 and serum bilirubin values from 0.6 to 2 mg. per cent. In all the diazo reactions were of the indirect type. None of the cases presented dye retention. In three cases in which remissions were induced by liver diet, subsequent estimations gave normal results. The hyperbilirubinemia occurring in pernicious anemia has been universally accepted. McNee²⁸ explained the excess of bilirubin which gives the indirect reaction on the basis of supersaturation of the serum resulting from excessive destruction of erythrocytes to such a degree that the excretory power of the liver is exceeded.

28. McNee, J. W.: Quart. J. Med. 16:390, 1923.

In the period of remission as induced by liver diet, the return to normal values would be expected on the basis of McNee's explanation indicating a decrease in the hemolysis. It would seem, then, that icterus from bilirubinemia which gives the indirect reaction and negative dye test is characteristic of a hemolytic process. This combination of results does not indicate so much a disease process in the liver itself as it measures the excretory efficiency of the reserve power of the liver under stress.

In four cases of hemolytic icterus, latent icterus ranging from 16 to 30 occurred with indirect serum bilirubin values of from 2.1 to 3.8 mg. per cent. In these cases as in pernicious anemia, there was no retention of dye. In all cases there was increased fragility of the erythrocytes. In two cases in which splenectomy was done, the weights of the spleen were 650 and 750 Gm. The serum bilirubin dropped from 2.9 to 0.5 mg. per cent and from 3.8 to 0.45 mg. per cent following splenectomy.

TABLE 11.—*Results in Normal Cases*

Number of Cases	Serum Bilirubin	Number of Cases	Icterus Index
38.....	—0.2	3.....	2
33.....	0.2 to 0.29	41.....	3
16.....	0.3 to 0.39	20.....	4
9.....	0.4 to 0.49	23.....	5
2.....	0.5 to 0.6	13.....	6
1.....	0.6 to 0.7		
1.....	0.7 to 0.8		
1.....	1.8 mg. per cent		
	Average 4.02		

SUMMARY

The measurement of serum bilirubin in 100 apparently normal cases by means of the quantitative van den Bergh reaction gave values ranging from a minimum of less than 0.2 mg. per cent to a maximum of 1 mg. per cent, with, however, the largest portion (87 per cent) with readings of less than 0.4 mg. per cent. In the same cases the average icterus index reading was 4.02, with a minimum reading of 2 and a maximum of 6. In all these cases, 2.2 mg. of bromsulphalein, injected intravenously, was removed from the serum in thirty minutes, without either systemic or local reactions.

Retention of dye and bilirubin occurred regularly in the cases of passive congestion of the liver resulting from cardiac decompensation.

The results obtained in various types of lesions of the heart showed no great difference. Though collectively the readings showed an inclination to be on a slightly higher level in mitral lesions, the individual variations was not sufficient to be of diagnostic value.

In catarrhal jaundice and in the jaundice following the use of arsenicals and alcohol, a high degree of retention of both dye and

bilirubin was obtained. The bilirubin from these various types of jaundice gave no characteristic difference in their behavior to the diazo reagent.

In all diseases of the gallbladder associated with frank jaundice, retention of dye occurred, but not in the cases in which a latent icterus was present. Not all cases of proved disease of the gallbladder showed a latent icterus.

Low values of serum bilirubin occurred in carcinoma in general. High values were encountered in cases in which metastases caused an obstructive jaundice.

In cirrhosis of the liver the serum bilirubin tests gave unexpectedly low values compared to the high degree of dye retention.

In cases of hemolytic icterus and pernicious anemia, an increase in the serum bilirubin was noted with an indirect diazo reaction and a negative dye test. Splenectomy in two cases of hemolytic icterus was followed by a return of the serum bilirubin to normal.

CONCLUSION

The use of bromsulphalein in the doses usually employed is devoid of local or systemic reaction. The retention of this dye occurs only in diseases of the liver.

The modification of the icterus index as suggested by Murphy commends itself for simplicity without the sacrifice of accuracy. The icterus index gives a numerical index of the degree of yellow discoloration of the serum, which may result from disease of the liver or disturbances in the bilirubin metabolism apart from the liver.

The diazo reagent differentiates between the bilirubinemia occurring as a result of disease of the biliary system, whether intrahepatic or extrahepatic, and the bilirubinemia occurring in disturbances of the reticulo-endothelial system characterized by increased destruction of erythrocytes.

These tests give an index of the vital metabolic functions of the liver only so far as these functions are paralleled by the excretory functions.

The tests are a valuable addition to the diagnostic equipment, but, like laboratory tests generally, are subject to wide variations in interpretation.

Book Reviews

THE FEMALE SEX HORMONE. Part I. Biology, Pharmacology and Chemistry. Part II. Clinical Investigations Based on the Female Sex Hormone Blood Test. By Robert T. Frank, A.M. M.D., F.A.C.S., Gynecologist to Mount Sinai Hospital, New York. Price, \$5.50. Pp. 331, with 86 illustrations and 36 graphs. Springfield, Ill.: Charles C. Thomas, 1929.

The author says "In this monograph there is no thesis to defend. The sole object actuating me is to present our present state of knowledge as far as is warranted by actual, proved facts." He has successfully adhered to this ideal on every page of this valuable monograph. The book falls naturally into two main divisions: First, a succinct summary of the physiology and biochemistry of the ovarian hormones to date. Second, a clear account of the physiology and physiologic pathology of the ovaries and the uterus in women, and the attempts to control and otherwise influence these processes by organotherapy. The book represents the material and conclusions of twenty-five years of laboratory work and clinical experience. The author has persisted in laboratory research and controlled clinical work for this long period despite discouragement that would have paralyzed or silenced most men not driven by the rare and unsatiable curiosity for truth. In this period he has stimulated a number of other workers in the field to undertake such phases of the work that he could not carry out personally, notably the biochemist Dr. R. G. Gustafson.

The author has subjected most of the ovarian preparations now on the market to biologic and clinical assays for activity, and, as was to be expected, in the hands of a competent worker, all of the ovarian preparations to be taken or administered by mouth proved inert. He says, "I have repeatedly put myself on record as entirely sceptical concerning the effect of desiccated, unconcentrated ovarian preparations, and yet the literature teems with glowing reports of the efficacy and the wonderful results obtained with these same biologically inert preparations. These effects vary from the immediate induction of menstruation after long periods of amenorrhea, the complete abolition of annoying and distressing menopause symptoms, to the complete relief of the intractable vomiting of pregnancy, etc. I am unable to account for this irreconcilable discrepancy between biological titer and clinical results, except on the basis of psychical effect, lack of strict criteria and control, and the optimism of both patient and physician."

One of the outstanding puzzles in the present problem is finding in the blood and urine of normal males (man) and in extracts of various plant tissues substances which on injection into spayed rodents or sexually immature rodents produce the same changes in the histology of the vaginal smears as are produced by the ovarian sex hormone. This would seem to indicate that we have to fall back on the ability to produce menstruation and the secondary sex characters in spayed primates as the only reliable biologic assay of the ovarian hormone.

The book is readable and clear. It may be perused with profit by every internist and general practitioner, and the biologic worker in this field will find it a useful source of reference.

DIE GASTROSKOPIE IN RAHMEN DER KLINISCHEN MAGENDIAGNOSTIK. VON DR. KURT GUTZEIT, Privatdozent an der Universität Breslau. Sonderausgabe des gleichnamigen Beitrages in "Ergebnisse der inneren Medizin und Kinderheilkunde." Volume 35. Price, 9/60 Rm. Pp. 94. Berlin: Julius Springer, 1929.

This brief monograph constitutes a real contribution to the literature of gastroenterology. It is not a manual of gastroscopy, but a discussion of gastric pathology based on the author's own experience. The first twenty-seven pages are devoted to a consideration of the various types of gastroscopes, their advantages and dis-

advantages, the technic, the dangers and the contraindications. It is noteworthy that 500 patients were subjected to gastroscopic study without a single fatality. The remaining seventy pages present the results of a combined gastroscopic, roentgenologic and clinical study. All of the patients were examined roentgenologically as well as gastroscopically by the author himself using the most modern roentgenologic technic. The majority were also observed clinically by him. In this way the results of the different methods were correlated in an effort to obtain as complete a picture as possible of the various disease processes. The discussion centers on gastritis, defects of the mucous membrane and ulcer. The author concludes that the three are indistinguishable symptomatically, that gastritis occurs commonly in the absence of gross mucosal defects, that acute ulcers may or may not be accompanied by gastritis and that gastritis, if present, may be in a different region of the stomach than the acute ulcer. Chronic ulcer, on the other hand, is invariably accompanied by gastritis. The first stage in the healing of an ulcer is a subsidence of the inflammatory reaction. No relationship exists between the severity of the pain and the degree of mucosal alteration either in gastritis or in ulcer.

The diagnosis of gastric carcinoma is discussed and the importance of the various criteria evaluated. Benign gastric tumors are considered. Special attention is given to the problem of gastric pain and to the relationship between mucosal changes and gastric acidity.

The monograph is highly recommended to all those interested in gastric disorders.

THE BIOCHEMISTRY OF THE AMINO-ACIDS. H. H. MITCHELL, and T. S. HAMILTON. American Chemical Society Monograph Series, No. 48. Price, \$9.50. New York: The Chemical Catalog Company, Inc.

The authors of this monograph have successfully dealt with the knowledge centering around the amino-acids in a complete and critical manner. They not only have attempted to order the facts about the amino-acids but have assuredly attempted a critical discrimination and reconciliation of conflicting data and theories.

Approximately, the first third of the monograph is devoted to an excellent description of the physical and chemical properties of the amino-acids, their determination in proteins and their individual identification. This section is well illustrated with photographs of the crystalline amino-acids. The tables listing their properties are clear, and the sources of the data are easily identifiable. Methods of determination referred to are described in general terms but not in detail because the authors wisely refrained from making this volume a laboratory guide.

The last two thirds of the book are devoted to the physiology of the amino-acids. The course of the amino-acids from their liberation in the gastro-intestinal tract to their absorption, utilization and final fate is fully discussed. When the work of investigators has been extensive and has had a profound influence on modern points of view, it is discussed in sufficient detail for the reader to gain a clear understanding of the points at issue. Much of the last portion of the book is devoted to problems associated with the metabolism of proteins with particular attention to their nutritive values. At first one gains the impression that this material is irrelevant to the primary purpose of the book, but the reviewer found that, although necessarily curtailed as to detail, this discussion really rounded out what one wanted to know about the place of amino-acids in the field of biology.

The bibliography is extensive, and the book is well indexed.

STERILIZATION FOR HUMAN BETTERMENT. A SUMMARY OF RESULTS OF 6,000 OPERATIONS IN CALIFORNIA, 1909-1929. By E. S. GOSNEY, B.S., LL.B., and PAUL POPENOE, D.Sc. Price, \$2. Pp. 201, with index and bibliography. New York: The Macmillan Company, 1929.

This is a timely, accurate and useful digest of the results of the 6,255 eugenic sterilizations in the state of California since the law came into force in 1909. California has the longest continuous record of eugenic sterilization of any state

or country. Dr. Dickinson, Secretary of the Committee on Maternal Health, New York, after an investigation of the operation of the sterilization law of California, stated: "The serious consideration given to the individual patient and the skill in operative work makes the experience in this state very weighty evidence on the whole problem." The authors have succeeded in summarizing the essentials of this experience clearly, objectively and remarkably free from propaganda. In California the operative mortality has been extremely low. A small percentage of the men and women sterilized showed return of fertility. The operation has no untoward effects on the sex life. In California the application of the sterilization law must have been in the hands of the ablest physicians and officials, for we are told that opposition to the law, even among the classes sterilized, is less and less in evidence. "A large part of the public is ready to accept sterilization for itself as well as for others—so much so that a purely permissive and voluntary law would cover most operations."

The first part of the book is devoted to a summary of the facts; the second part to conclusions and general considerations, and the appendixes contain much useful historical and statistical data.

PATHOGENIC MICROORGANISMS. By W. H. PARK, A. W. WILLIAMS and C. KRUMWIEDE. Ninth edition revised. Price, \$6.50. Pp. 819. Philadelphia: Lea & Febiger.

The ninth edition of the Park, Williams and Krumwiede "Pathogenic Microorganisms" scarcely needs an introduction to students and workers in bacteriology. For many years the previous editions of this text have been accepted as a standard guide, and the ninth edition ranks with the others. The arrangement of the chapters into three parts is continued in the new edition but with some slight changes. The first part deals with the methods for studying bacteria. Procedures for sterilization, for the preparation of many mediums, for culturing bacteria and for carrying out immune reactions are described in detail and with ample discussions. This part also includes the technic for the complement-fixation tests and the Kahn and the Meinicke tests.

In the second part consideration is given to the individual pathogenic microorganisms, the bacteria in particular, the protozoan parasites and the vegetable forms higher in organization than the bacteria. The chapters on the molds and the yeasts are probably the least satisfactory of the book, and could be improved considerably. Many details of technic and valuable discussions are contained in the chapters of the second part, as well as accounts of diseases produced by filtrable viruses.

Part three deals with applied microbiology, and the chapters therein concern such matters as the bacteriologic examination of water, air, soil, milk, the contamination and purification of water and the standardization of disinfectants.

MEDIZINISCHE PRAXIS. BAND V. RADIUMTHERAPIE, METHODEN UND AUSSICHTEN. VON DR. F. GUDZENT, a. o. Professor an der Universität Berlin. Herausgegeben von Grote, Fromme, Warnekros. Paper. Price, 6.50 marks. Pp. 116, with 53 illustrations. Leipzig: Theodor Steinkopff, 1929.

This booklet serves as a short, concise handbook of reference regarding the indications and usage of radium in medicine. A short résumé of the discovery of radium and of its physical and chemical properties is given. The decay of radium and its emanation is explained, and filtration principles with various types of radium applicators are illustrated and explained.

The biologic response of skin, muscle, tendon, cartilage, bone, nerve tissue and the blood to the action of the rays from radium is reported.

Indications and technic of treatment for gout, rheumatism, neuritis, dyscrasias of the blood and chronic suppuration by inhalations of emanation and by drinking

and bathing in radio-active waters are given; a discussion of the radium content of the waters of various popular German watering places is also included.

The types of lesions of the skin amenable to the action of radium are briefly discussed; for deeper tumors the importance of combined surgical intervention and usage of radium is stressed. The gynecologic uses of radium are fully entered into.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Associate Professor of Medicine, University of Arkansas, Little Rock, Ark. Fifth edition. Cloth. Price, \$10. Pp. 817, with 310 illustrations and three colored plates. St. Louis: C. V. Mosby Company, 1927.

This book, which has been long recognized as one of the standard texts in the subject, now appears in its fifth edition, rather extensively revised and rewritten in many portions, particularly those dealing with the pathologic physiology of the heart and the manifestations of incipient cardiac insufficiency. The illustrations are well chosen and clear, being printed on good paper, and being accompanied by brief explanatory captions, thereby enabling the student to grasp the context readily.

The chapters on examination of the nervous system are too sketchy to be of much value. This, however, is beyond the scope of the usual textbook on physical diagnosis.

This manual is recommended to medical students and practitioners.

DISEASES OF THE STOMACH, A TEXTBOOK FOR PRACTITIONERS AND STUDENTS. By MAX EINHORN, M.D., Emeritus Professor of Medicine at the New York Post-Graduate Medical School and Hospital, Consulting Physician to the Lennox Hill Hospital. Seventh revised edition. Price, \$6 net. Pp. 576. New York: William Wood & Company.

This is a new edition of an old book, a thorough text of the old type, abounding in such terms as acute and chronic gastric catarrh, gastrosuccorrhea, myxorrhea gastrica, gastrohydrorrhea, ischochymia, parorexia, choria, sitophobia, gastralgia, gastralgokenosis, hypanakinesis ventriculi, hyperanakinesis ventriculi and peristaltic restlessness of the stomach. Local treatment of the stomach is thoroughly considered, including the gastric douche and spray, the stomach powder blower and the various forms of the electric therapy. The work is essentially clinical. In the opinion of the reviewer, modern gastric physiology and roentgenology should receive much more consideration than is given them.

EXPERIMENTAL EDEMA (NEPHROSIS) IN DOGS IN RELATION TO EDEMA OF RENAL ORIGIN IN PATIENTS *

M. HERBERT BARKER, M.D.

CHICAGO

AND

E. J. KIRK, M.D.

OMAHA

For many years a keen interest and much controversy have developed over the views of von Müller,¹ Munk,² Volhard and Fahr³ and Epstein,⁴ concerning the condition that they have termed nephrosis.

For the past two years we have had the opportunity to study the cases of nephritis with edema in the wards and at the renal clinic of the Peter Bent Brigham Hospital in Boston. Most of these cases have shown fairly constant and comparable conditions generally regarded as typical of nephrosis. They were characterized by oliguria, albuminuria, relatively noncellular urine sediment, edema, normal renal function as measured by several tests, usually normal blood pressure, a lowered metabolism and a chemical blood picture, which consisted of low serum protein, reversed albumin-globulin ratio, increased blood cholesterol, phosphorus and fibrinogen and a decreased blood calcium.

During the course of our study in the renal clinic, three cases were observed which were unusual and, to us, of particular interest. All three patients had had acute nephritis which apparently had subsided except for the continued loss of a large amount (from 6 to 15 Gm. per day) of albumin in the urine. All were on a restricted protein intake. Studies of the blood showed a gradual fall in the serum proteins, and later the appearance of edema, together with all of the observations regarded as characteristic of nephrosis. We were impressed by the

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* From the Medical Departments of the Peter Bent Brigham Hospital and Harvard Medical College.

* Read in part before the Harvard Medical Society, Feb. 21, 1929.

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2. Munk, F.: *Nierenerkrankungen*, Berlin, Urban & Schwarzenberg, 1925.

3. Volhard, Franz, and Fahr, T.: *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

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constant association of this well marked albuminuria with the characteristic blood serum picture. We noticed that the greater the albuminuria, the lower was the serum protein, and the lower the serum protein, especially the albumin fraction, the greater was the edema. This led us to wonder whether the whole symptom-complex of nephrosis might not be secondary to the low serum protein. In order to determine this point, we have attempted to produce in dogs a serum picture analogous to that found in these patients. As a result the following procedure was devised.

METHOD

Four young adult dogs were selected and kept under observation during a control period varying from one to six weeks. During this period the animals were trained so that all of the procedures could be done readily on them without the use of any form of anesthetic, narcotic or sedative. Plasmapheresis⁵ was the method of choice to produce a low proteinemia. The dogs were bled at intervals varying from four to sixty-eight days and in total amounts varying from 3,750 cc. to 42,500 cc. The blood was centrifugated, the serum discarded and the cells reinfused mixed with Locke's solution. One liter of warm saline was given by stomach tube a short time before the operation to prevent shock. The bleeding was done by puncture of the femoral arteries, and reinfusion was done into any available vein. All procedures were done with strictly aseptic technic, and at no time was there any evidence of any form of infection, except for a slight infection in dog 1 following nephrectomy.

The total serum protein, serum albumin and serum globulin determinations were done by the combined methods of Howe,⁶ Wu,⁷ and Kock and McMeekin,⁸ as described by Hawk and Bergeim;⁹ blood cholesterol as described by Bloor, Pelkan, and Allen;¹⁰ blood phosphorus by the method of Fiske and Subbarow;¹¹ blood calcium by the method of Clark and Collip;¹² fibrinogen by the method

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of Foster and Whipple;¹³ blood volume by the method suggested by Keith, Rowntree, and Geraghty¹⁴ with the modification of Murphy, Monroe, and Fitz;¹⁵ cell volume by the method of Haden.¹⁶ The basal metabolism was done with the Benedict-Roth machine, by means of the Blalock mask;¹⁷ the cardiac output according to the Fick principle¹⁸ and the oxygen and carbon dioxide content of the arterial and the venous blood, drawn directly from the right and left sides of the heart, were done with the manometric apparatus of Van Slyke and Neill.¹⁹

PROTOCOL

Dog 1 was a male shepherd that weighed 19.2 Kg. Observations on this animal may conveniently be divided into four periods: (1) preliminary control period of one month; (2) first period of plasmapheresis up to nephrectomy (ninety-two days); (3) period of convalescence, one month during which there was no plasmapheresis and (4) second period of plasmapheresis of twenty-four days.

In the control period urinalysis, blood pressure, urea nitrogen of the blood and phthalein tests were normal. The cholesterol was considered above the normal of from 80 to 100 mg. per hundred cubic centimeters. The serum albumin fraction was slightly below normal (table 1).

Plasmapheresis was then begun and continued at varying intervals over a period of ninety-two days up to the time at which nephrectomy was done. The daily amount of blood removed ranged from a minimum of 400 cc. to a maximum of 1,500 cc. The total amount of blood removed during this period was 18,000 cc. On the thirty-eighth day edema of the extremities occurred, and was maintained irregularly during this second period. The edema varied from slight pitting of the extremities to generalized anasarca. The weight increased as edema accumulated. The greatest increase was 2.7 Kg. During the experimental period, weakness and muscular wasting with a decrease in weight of 1.2 Kg. during the edema-free stages were noted. On the forty-third day, albumin, hyaline and granular casts appeared in the urine. During this second period the cholesterol rose to as high as 254 mg. per hundred cubic centimeters. The blood calcium dropped to 9.09 mg., and the phosphorus increased to 15 mg. per hundred cubic centimeters. The red blood count decreased to 4,100,000. The cell content of the blood measured by the hematocrit decreased to 21.85 per cent. No changes occurred in the blood pressure or renal function test. There was only a slight increase of the fibrinogen. The basal metabolic rate decreased from 156 to 112

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TABLE 1.—Summary of Observations on Dog 1*

Date	Wt.	Art.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Cn	P	Fld.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.O.	Bl.Vol.	Ed.	Leg Mens.	Comment
10/25/23	1.00; negative	110/ 70	55	13	170	10.69	8.1	41	6.02	2.52	3.50	191
11/27/23	10.2	450	110/ 70	174	6.82	2.18	4.34
11/28/23	...	450	110/ 60	..	21	251	4.30	...	5.3	...	5.31	0.72	4.62
11/30/23	18.6	450	110/ 60	6.1	41.7	6.37	2.49	3.88
12/ 4/20	18.0	450	4.16	...	6.1	11.0	5.50	1.26	4.39
12/ 6/23	17.6	0	Negative	130/ 80	...	22	164	4.2	100
12/10/23	...	450	138/ 80	...	17	184	4.3	4.29	1.61	2.68
12/11/23	4.68	1.63	3.05
12/12/23	...	450	Negative	4.67	1.12	3.55
12/16/23	18.0	700	Negative	15	...	9.69	2.6	...	5.3	...	5.07	1.20	3.87
12/18/23	...	700
12/20/23	10.0	700	150	+
12/20/23	19.0	700	Negative	17	100	9.34	5.10	0.67	4.13	142	+
12/23/23	18.0	700	163	0
1/ 2/29	18.4	700	Negative	110/ 60	...	14	125	9.54	21.8	4.03	0.63	3.40	++
1/ 3/29	18.7	700	++
1/ 4/20	20.2	700	Negative	121/ 60	4.02	0.61	3.38	127	++
1/ 5/20	...	0	122/ 60	++
1/ 7/20	19.2	750	Negative	10	0.3	4.38	0.81	3.57	156	0
1/ 8/20	19.6	750	+
1/ 9/29	...	750	++
1/10/29	20.0	750	++
1/11/29	20.3	750	Negative	4.68	0.60	3.19	++
1/12/29	20.4	750	++
1/13/29	20.0	0	++
1/14/29	19.2	750	Alb. 0; casts +	12	4.79	0.83	3.86	+
1/15/29	19.3	900	0
1/16/29	19.4	0	Alb. 0; casts +	0
1/18/29	19.2	0	Alb. 0; casts +	0
1/24/29	10.1	0	13 / 80	0
1/28/29	10.3	0	0
1/29/29	10.3	900,000	Alb. 0; casts +	0
1/30/29	20.6	900	Alb. +; casts +	5.13	0.97	4.26	0
1/31/29	20.4	900, 500	Alb. +; casts +	10.46	15	...	4.1	30.4	++
																				4.7	Edema of body wall 7; ascites

2/ 1/29	21.9	400	Alb. +; casts +	50	..	60	9.24	12	..	4.9	26.4	3.55	0.6	2.95	1.554	+++++	...	Generalized edema; ascites; slightly dyspnea
2/ 2/29	21.3	0	Alb. +	112	3.930	+++++	5.0	Nephrectomy (right kidney)
2/ 5/29	18.2	0	Casts +	18	4.87	0.88	4.01	135	0	3.2	Convalescent period
2/ 9/29	...	0	Alb. +; casts +	Slight superficial infection of wound
2/13/29	...	700	206	11.57	17	0.95	0.55	2.41	4.14	0	...	Wound healed; clean
2/22/29	17.6	0	Fat; casts	152/60	0	...	Second period of phlebotomies
3/ 5/29	17.3	450	Alb.; fat; casts	130	10.74	12	4.91	2.03	2.88	0	3.5	...
3/ 6/29	17.5	450	0
3/ 7/29	17.6	600	Negative	160/76	0
3/ 8/29	17.6	450	120	9.7	13	4.41	1.76	2.65	±	3.7	...
3/ 9/29	17.6	0	Alb.; casts	160/70	54	6.2	29.0	0
3/11/29	17.6	550	Alb.; casts	0
3/12/29	17.4	450, 450	Alb.; casts	11	132	4.89	1.57	3.31	0	3.5	Edema of legs and chest wall
3/13/29	...	450	Alb.; casts	+	3.7	...
3/14/29	17.6	450	Alb.; sp.gr. 1.010	++	4.0	...
3/15/29	17.7	550	Alb.; casts	120	12.0	15	..	6.1	30	3.60	1.39	2.21	+	3.7	...
3/18/29	17.1	600	196	10.65	5	1.1	3.95	1.82	2.13	0	3.2	Partial collapse
3/19/29	18.2	450	Casts	0
3/20/29	17.2	450	Alb.	0
3/21/29	17.5	450	Alb.; casts	0	3.2	Not responding to plasmapheresis
3/22/29	17.4	450	0
3/25/29	17.4	400, 400	8	..	9.71	4	4.88	1.64	3.24	0
3/26/29	18.3	450, 450	Negative; 1.010	220/100	0
3/27/29	19.1	450	Negative; 1.010	+
3/28/29	17.9	450	Alb.; casts	0
3/29/29	17.4	450	Alb.; casts	0	...	Animal killed (ether, 10 cc. intra-cardiac)

* The following explanatory terms are for all tables: Wt., weight in kilograms; Art. Sect., number of cubic centimeters of blood removed from femoral artery; B.P., blood pressure in millimeters of mercury; P.S.P., the phenolsulphonphthalein test for kidney function; Cho., milligrams of cholesterol per hundred cubic centimeters of blood; Ca., milligrams of calcium per hundred cubic centimeters of blood; P, milligrams of phosphorus per hundred cubic centimeters of blood; Fib., grams of fibrinogen per hundred cubic centimeters of blood serum; R.B.C., red blood cell count; Hem., hematocrit, percentage of red blood cells; T.P., grams of serum protein per hundred cubic centimeters of blood; Alb., grams of serum albumin per hundred cubic centimeters of blood; Glob., grams of serum globulin per hundred cubic centimeters; B.M.R., basal metabolic rate, calories per kilogram hour; Card.O., cardiac output, number of cubic centimeters of blood per minute; Bl.Vol., blood volume in cubic centimeters; Ed., edema; Leg Meas., circumference of hind legs in inches.

calories per kilogram hour at the time that there was generalized edema. The cardiac output increased to 3,930 cc. per minute, while the blood volume remained constant.

At the end of this period a right-sided nephrectomy was done, and the dog was allowed to convalesce for one month, during which time plasmapheresis was omitted. (The specimen of the organs of this as well as of all the other animals was placed immediately after nephrectomy and death in fixatives of formaldehyde, Zenkers' and Kaiserling's solution). There were 480 cc. of a clear, straw-colored fluid in the abdominal cavity. The right kidney was normal in size and appearance. The cortex and medulla measured 11 and 14 mm. in thickness, respectively. The capsule stripped easily and the surface appeared normal. On the cut surfaces grayish-yellow, bulging bands extending through the cortex were noted. Microscopically, the predominating lesion was a moderate degree of swelling of the tubules which in numerous instances were markedly damaged. Isolated tubules showing almost complete disintegration of the epithelium could be followed for considerable distance. In rare instances hyaline droplets were found in tubular epithelium and within the lumina of the tubules. There were also rare but definite areas of plasma cell infiltration in the cortical tubular region. A rare glomerulus showed hyalinization of Bowman's capsule. Appropriate stains brought out considerable fatty infiltration along the basement membrane of the tubules (fig. 8).

Plasmapheresis was resumed on dog 1 after one month of convalescence, and was continued for twenty-four days. At the beginning of this third period the dog weighed 17.3 Kg. The blood removed per day was a minimum of 450 cc. and a maximum of 900 cc.; the total amount removed was 10,400 cc. On the fourth day slight edema of the extremities occurred, but could not be maintained. The last nine days the dog was edema-free except for the twenty-second day when edema of the chest wall and neck region occurred. This disappeared on the following day and did not reform, although plasmapheresis was continued for two days more. The weight remained constant except for the twenty-second day when it increased to 19.1 Kg. Urinalyses showed that the specific gravity of the urine had fallen from 1.040 to 1.010. Albumin, hyaline and granular casts, fat droplets, small renal cells and occasionally slight traces of sugar were found. The blood pressure rose to 220 systolic and 100 diastolic. The urea nitrogen of the blood and phthalein tests remained normal. The blood cholesterol increased to 196 mg. The blood phosphorus rose to 15 mg.; but by the end of the experiment it had returned to a normal level of 4 mg. per hundred cubic centimeters. The fibrinogen rose to 1.1 Gm. per hundred cubic centimeters of serum. No remarkable change occurred in the calcium. The red blood cell count remained at the normal level of 6,240,000. The cell content of the blood as measured by the hematocrit was 29 per cent. At the end of this period the dog was killed and autopsy was performed. The left kidney weighed 57 Gm. The cortex and medulla measured 11 and 13 mm. in thickness, respectively. This kidney differed little in gross appearance and size from the right one, although the capsule was somewhat thicker. The cut surface showed the same grayish brown streaks, slightly more prominent than before, radiating through the cortical region to the surface. Microscopically, however, there was a marked difference in the two kidneys. The predominating lesion, as in the first kidney removed, was in the tubules. Swelling and tubular atrophy were marked. There were numerous areas of lymphoid and plasma cell infiltration and connective tissue replacement throughout the cortical tubular region. Many glomeruli showed thickening and hyalinization of the capsule with more glomerular atrophy than was seen previ-

ously. Special stains revealed rather marked fatty infiltration or degeneration of the tubules, and most of the glomeruli and capsules, too, showed fatty infiltration (fig. 9).

Dog 2 was a large male shepherd weighing 21 Kg. The preliminary control period was one week. All control studies were normal (table 2).

Plasmapheresis was then begun and continued at varying intervals for four months, with removal of a minimum of 450 and a maximum of 1,800 cc. per day, or a total of 42,500 cc. On the fifth day after plasmapheresis was begun, slight pitting edema of the legs was noted. As plasmapheresis was continued, generalized anasarca was observed. The edema varied in amount and time of occurrence, depending on the amount and frequency of plasmapheresis. During the last eighteen days the edema was maintained and was marked, but the amount and frequency of plasmapheresis had to be markedly increased. The weight during the period of marked edema increased to 25.8 Kg. During the edema-free periods the dog showed weakness and muscular wasting. On the thirty-second day after plasmapheresis, albumin, hyaline and granular casts, fat droplets, renal cells and occasional red blood cells were noted in the urine. After the third month of plasmapheresis, the specific gravity of the urine dropped to 1.010. Slight traces of sugar were found in the urine occasionally. The blood pressure gradually rose to 170 and 190 systolic, and to 90 and 110 diastolic, but was not constant. The urea nitrogen of the blood and results of the phthalein tests remained normal. The blood cholesterol increased to 180 and 216 mg. The blood calcium decreased to 8.22 mg. The blood phosphorus rose to 17 mg., and the fibrinogen rose to 1.4 Gm. per hundred cubic centimeters of serum. The red blood cells decreased to 3,350,000. The hematocrit, cell content of the blood, dropped to 20.1 per cent. The basal metabolic rate showed a decrease to as low as 123 calories per kilogram hour during the edematous stages. The cardiac output increased during the period of marked edema to as high as 7,820 cc. per minute. No remarkable change occurred in the blood volume. At the end of the fourth month, the dog was killed for pathologic study. The right kidney weighed 66 Gm. and the left 62 Gm. The cortex and medulla were 10 and 14 mm. in thickness, respectively. Grossly, the kidneys showed slightly thickened capsules which stripped with a little more difficulty in comparison with the others. The surface of the kidneys showed small white patches which formed scattered depressions on the surface. The cut surface showed an area of marked scar formation which appeared to be 3 or 4 mm. in thickness throughout the tubular region. From this diffuse scar area there were bands radiating through the cortex which caused the dimpling and scarring of the surface already described. Between these bands were yellow colored patches which proved to be fat. Microscopically, the tubules showed marked cloudy swelling with desquamation of the epithelium and marked tubular atrophy. In the tubules, hyaline and fatty casts were noted. There were linear areas of marked lymphoid and plasma cell infiltration accompanying the area of scar tissue replacement throughout the tubular region. Where these areas of connective tissue and small round cell infiltration encircled the glomeruli, the latter were atrophied and showed marked thickening of the capsule (fig. 10). Specially stained frozen sections showed some fatty infiltration of the tubules, but was not so marked as that observed in dogs 1 and 4.

Dog 3 was a large male shepherd that weighed 23 Kg. The preliminary control period was six weeks. During this time studies were repeatedly made as described previously. Results of urinalyses, blood pressure readings, renal function tests, and blood studies were normal. At the end of this period, plasmapheresis was done on four successive days, with removal of a minimum of 675

TABLE 2.—Summary of Observations on Dog 2

Date	Art. Sect.	Wt.	Urine	B.P.	P.S.P.	B.U.N.	Chol.	Ca	P	Fib.	R.B.C.	Hem.	T.P.	Alb.	Glob.	B.M.R.	Card.	O. Bl.	Vol.	Ed.	Leg Meas.	Comment
12/ 6/28	Negative	138/ 80	60	22	100	10.20	...	1.3	5.4	31.6	Control period
12/10/28	...	21.0	Negative	160/ 80	..	15	4	5.96	2.00	3.96	Condition good
12/13/28	Sp. gr. 1.040	6.02	2.01	3.88	Plasmapheresis
12/14/28	450	21.8	Negative	1.4	...	36.8	Plasmapheresis
12/15/28	450	4.67	0.94	3.93	Plasmapheresis
12/16/28	Negative	Plasmapheresis
12/18/28	750	22.8	Negative	15	90	...	9.6	4.59	0.90	3.64	Plasmapheresis
12/20/28	...	22.2	166	+	Plasmapheresis
12/22/28	750	22.8	164	0	Plasmapheresis
12/26/28	750	20.8	Negative	15	95	9.90	8.9	5.40	0.85	4.54	0	Plasmapheresis
12/28/28	750	20.8	Negative	0	Plasmapheresis
12/31/28	750	20.0	Negative	0	Plasmapheresis
1/ 1/29	750	20.4	Sp. gr. 1.042	160/110	...	15	116	9.14	5.4	30.0	4.65	0.98	3.67	+	Edema of extremities
1/ 3/29	750	20.4	+	Edema of extremities
1/ 4/29	750	21.0	3.91	0.70	3.21	+	Edema of extremities
1/ 7/29	750	21.0	...	158/ 90	...	13	0.55	4.88	0.55	4.32	+	Edema of extremities
1/ 8/29	750	21.2	+	Edema of extremities
1/ 9/29	750	+	Edema of extremities
1/10/29	750	21.0	Negative	+	Edema of extremities
1/11/29	750	21.2	+	Edema of extremities
1/12/29	750	21.6	+	Edema of extremities
1/14/29	750	20.1	14	5.00	0.90	4.10	+	Edema of extremities
1/15/29	900	21.3	+	Edema of extremities
1/16/29	0	20.5	Negative	145	0	Edema of extremities
1/17/29	Casts	154	2,950	1,960	0	Edema of extremities
1/21/29	...	20.6	106	10.65	14	0.3	...	24	4.69	0.83	3.86	137	2,200	2,042	0	Edema of extremities
1/22/29	900, 900	22.0	Casts	2.75	0.80	2.25	0	Edema of extremities
1/23/29	900, 900	23.6	+	Edema of extremities
1/24/29	900	23.4	+	Edema of extremities
1/25/29	900	22.3	+	Edema of extremities
1/27/29	0	22.4	1.2	+	Edema of extremities
1/28/29	900	21.4	184	3,900	2,040	+	Edema of extremities
1/29/29	900	21.6	Casts	+	Edema of extremities
1/30/29	900	22.6	Alb. +; casts +	60	9.34	17	0.8	3.29	0.74	2.55	+	Edema of extremities
1/31/29	900	22.9	Alb. +; casts +	9.15	+	Edema of extremities
2/ 1/29	900	23.6	Alb. 0; casts +	3.8	17.7	2.82	0.41	2.41	+	Edema of extremities
2/ 5/29	0	21.6	Alb. +; casts +	216	10.64	5.26	0.95	4.31	127	2,920	2,266	0	Edema of extremities

2/ 7/29	21.2	900	Alb. +; casts +	213	10.18	15	0.4	5.34	0.90	4.44	0	...
2/13/29	700	190	9.81	19	0.5	5.13	2.06	3.07	0	...
2/18/29	675	Alb. +; casts +	189	10.81	16	4.56	2.09	2.47	0	...
2/21/29	22.3	900	Alb. +; casts +	196/110	..	100	9.78	12	...	4.0	23.3	3.17	1.57	1.60	157	2,700	0	...
2/23/29	21.6	0	190/120	..	100	4.71	13	3.57	1.87	1.70	193	2,700	0	...
2/25/29	22.6	700	0	...
2/26/29	22.4	900	Casts +; fat +	0	...
2/27/29	23.1	900	0	...
2/28/29	900, 900	Casts +	0	...
3/ 1/29	24.5	900	Casts +	115	8.22	10	1.90	0.58	1.32	+	3.7
3/ 2/29	24.1	0	Negative	0.5	5.3	26	151	6,220	1,759	++	4.0
3/ 4/29	24.1	900	0	...
3/ 5/29	24.1	900	10	9.15	14	3.33	1.49	1.84	0	...
3/ 6/29	23.8	900	Casts +	++	4.5
3/ 7/29	23.6	900	Alb. +; casts	144/ 70	++	5.5
3/ 8/29	23.8	900	111	9.34	13	...	4.4	27.7	2.95	1.12	1.83	++	5.0
3/ 9/29	21.3	0	160/ 90	35	146	3,870	1,659	++	4.5
3/11/29	21.2	900	Negative; 1.010	0	...
3/12/29	21.2	675, 900	Casts +	116	3.36	1.24	2.02	+	3.8
3/13/29	24.8	900	Casts +	++	4.5
3/14/29	25.0	900	Casts +	++	4.0
3/15/29	25.0	900	Casts +	100	11.20	17	2.90	0.69	1.91	++	5.5
3/16/29	21.6	0	3.3	19.6	164	7,150	++	5.7
3/18/29	22.1	850	188	10.65	5	3.08	1.41	1.67	0	3.7
3/19/29	23.7	900	Alb. +; casts +	±	4.2
3/20/29	23.7	900	±	4.2
3/21/29	23.8	900	Negative	++	...
3/22/29	24.0	900	Sp. gr. 1.010	++	...
3/25/29	22.0	900, 900	10	9.53	4	3.97	1.26	2.71	0	3.7
3/26/29	23.6	900, 900	Casts +; fat +	168/ 90	+	...
3/27/29	25.1	900	++	5.0
3/28/29	21.9	900	Alb. +; casts +	80	6.6	...	1.1	2.80	0.63	2.17	++	5.7
3/29/29	21.4	900	Casts +; fat +	20.4	++	5.1
3/30/29	25.2	900	Alb. +; casts +	++	5.0
3/31/29	21.2	900	++	4.0
4/ 1/29	21.2	700, 700	Casts +; fat +	++	...
4/ 2/29	24.6	800, 800	Alb. +	++	...
4/ 3/29	25.8	900	Alb. +; fat +	10	9.62	3.3	20.1	2.76	0.85	1.91	123	7,520	2,320	++	...

Marked edema; ascites

Marked edema; ascites

Generalized anasarca

Animal killed (ether, 10 cc. Intracardiac)

cc. and a maximum of 1,500 cc. of blood per day, or a total of 3,720 cc. At the end of this time, a well marked edema of the extremities and scrotum appeared. Albumin, hyaline and granular casts were found in the urine. No changes occurred in the blood studies (table 3). The dog died suddenly due to collapse.

The kidneys of this dog illustrate our earliest stage in the progressive kidney lesion observed in this series of animals. The kidneys weighed 60 Gm., the cortex 9 mm. and the medulla 15 mm. Grossly, there was no variation from the normal. Microscopically, the tubules showed cloudy swelling with slight desquamation of the epithelium in the convoluted portions. The glomeruli were normal except for a precipitate (possible albumin) seen in the capsular spaces, streaming down into the tubules (fig. 11).

Dog 4 was a male bull that weighed 15 Kg. The preliminary control period was two weeks. Urinalyses, blood pressure, phthalein test, blood studies, basal metabolism, cardiac output, and blood volume were all normal. Plasmapheresis was then begun and continued for ten days with removal of a minimum of 200 cc. and a maximum of 900 cc. of blood per day, or a total of 4,925 cc. On the third day edema occurred, and this was maintained for two weeks. The maximum weight was 15.9 Kg. on the twelfth day, and the minimum 12.7 Kg. on the eighteenth day after plasmapheresis was begun. Slight muscular wasting and loss of strength was observed during the experiment. On the seventh day of plasmapheresis, albumin, hyaline casts, fat droplets and renal cells appeared in the urine. No changes were observed in the blood pressure, renal function test, cholesterol or fibrinogen. The blood calcium decreased to 8.9 mg., and the blood phosphorus rose to 12 mg. per hundred cubic centimeters. The red blood count dropped to 4,690,000, and the cell content of the blood as measured by the hematocrit, to 26.3 per cent. The total serum protein, serum albumin and serum globulin dropped to as low as 3.06, 1.02 and 2.04 mg. per hundred cubic centimeters, respectively. The metabolic rate decreased to 193 calories per kilogram hour, but returned to normal by the end of the rest period. The cardiac output increased to as high as 4,070 cc. per minute, while the blood volume remained at the normal level (table 4).

One month after discontinuing the plasmapheresis, the animal was killed, and an autopsy was performed to determine whether kidney repair had taken place. The right kidney weighed 56 Gm., the left 59 Gm., the cortex 9 mm., and the medulla 15 mm. Grossly, the kidneys were normal in size and appearance. The cut surface revealed grayish-brown streaks radiating out toward the capsule. Microscopically, cloudy swelling and some hyaline droplet formation with desquamation of the epithelium and extrusion of the nuclei were observed in the convoluted portions. The tubules contained occasional hyaline and fatty casts. Scattered at infrequent intervals were areas of small round cell and plasma cell infiltration. Occasionally, a glomerulus showed marked atrophy, hyalinization and thickening of the capsule, while many of the others showed apparent enlargement of the capillary tufts. Special fat stain revealed marked fatty infiltration of the tubules and occasionally of the glomeruli (figs. 12 and 13). Many of the tubules appeared normal. Occasional mitotic figures possibly indicating regeneration were found in the tubular epithelium.

Studies of the other tissues of these dogs, such as thyroid, heart, liver, spleen, adrenals, etc., showed no abnormalities except for a possible increase of the connective tissue in the spleen and liver of dogs 1 and 2. All of the dogs except dog 1 were killed immediately by the injection of 10 cc. of ether, directly into the heart.

TABLE 3.—Summary of Observations on Dog 3

Date	Wt.	Art. Sect.	Urine	B.P. 130/ 70	P.S.P. B.U.N. Chol.	Ca	P	Fib.	R.B.C. Hem.	T.P.	Alb.	Glob.	B.M.R. Card.O. Bl.Vol.	Ed.	Leg Meas.	Comment
1/ 9/29	23.0	...	Negative	...	14	55	5.82	1.75	4.17	3.5	Condition fair; nutrition poor
1/12/29	23.6	...	Negative	166
1/17/29	23.8	...	Negative	74	26.4	188.6	1,674	...	Bronchitis; coughing
1/21/29	23.7	18	..	22.0	5.26	1.18	4.08	183	2,755	3.5	Anemic; condition poor
1/23/29	23.6	3.8	20.0	2,160
1/25/29	23.0	...	Negative	100	19	6.34	1.23	5.11	Condition improving
2/ 5/29	23.0	5.4	...	6.53	2.32	4.24	171	2,000
2/ 8/29	23.5	...	Negative	...	10	5.8	26.3	190	2,441
2/11/29	22.3	...	Negative	227	2,485	...	Shown only for pathologic study
2/15/29	22.3	...	Negative	228	7,570	...	Symptoms of hemorrhage
2/18/29	22.3	675	Negative	Partial shock
2/19/29	...	700, 800	Negative	3.5	...
2/20/29	...	800	Alb. 0; casts +	++	3.75	...
2/21/29	22.5	800	Alb.; casts	60	11	..	23.2	5.07	2.98	2.00	...	++	4.12	Sudden collapse

TABLE 4.—Summary of Observations on Dog 4

Date	Wt.	Art. Sect.	Urine	B.P. 120/ 80	P.S.P. B.U.N. Chol.	Ca	P	Fib.	R.B.C. Hem.	T.P.	Alb.	Glob.	B.M.R. Card.O. Bl.Vol.	Ed.	Leg Meas.	Comment
2/ 7/29	15.4	...	Negative	...	55	13	4	6.78	3.29	3.49	General condition good
2/22/29	15.1	129	245
2/23/29	14.2	...	Negative	140/ 78	12	0.65	35.4	6.51	2.72	3.79	250	1,644	3.25	Plasmapheresis
2/25/29	15.1	450	40	Dyspnea
2/29/29	15.2	675	Negative	8.5	3.06	1.02	2.04	2,530	Pitting of ankles
2/27/29	15.3	450, 450	112	...	5.3	25.8	±±	4.0	Edema of legs, prepuce and scrotum
2/28/29	14.0	450	++	4.5	...
3/ 1/29	14.6	600	0.45	229	1,511
3/ 2/29	14.6	0	Alb. +; casts	±	4.3	...
3/ 4/29	...	400	10	...	12	3.56	1.04	2.52	...	++	4.7	...
3/ 5/29	...	400	Negative	8.97	++
3/ 6/29	14.5	400	Alb. 0; casts	112/ 70	++
3/ 7/29	14.6	200	111	10	3.76	1.30	2.46	...	++	4.7	Asclites; "rest period"
3/ 8/29	14.7	450	10.37	4.6	193	1,500
3/ 9/29	15.9	0	Negative	++
3/10/29	15.0	0	Negative	110/ 68	65	++	3.5	...
3/11/29	15.0	0	Negative	+
3/16/29	12.7	130	9	...	3.4	5.83	2.80	3.03	250	1,330	...	Animal killed (10 cc. ether intracardiac)
4/ 6/29

COMMENT

In this group of dogs, the removal of from 400 to 900 cc. of blood with the re-infusion of the cells from four to six times per week resulted, as the tables show, in gradual decrease in their serum protein. This reduction of the total protein occurred chiefly at the expense of the albumin fraction with a fairly rapid development of a reversion of the albumin-globulin ratio (fig. 1). After from four to six weeks of this continued loss of serum protein, the total blood protein was near 4.3 Gm., and the globulin fraction had increased to 3 or 3.3 Gm., while the albumin fraction had fallen to about 1 Gm. per hundred cubic centi-

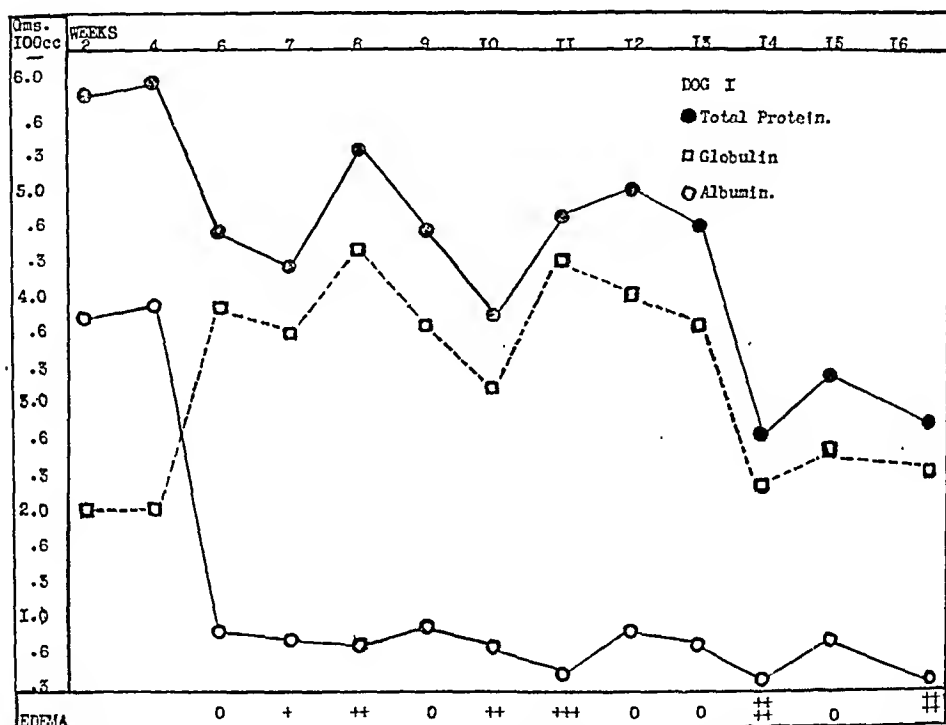


Fig. 1 (dog 1).—Chart illustrating the gradual changes of the total serum protein, the albumin and globulin fractions during plasmapheresis. By the sixth week the albumin-globulin ratio became inverted. By the seventh week there was a profound drop of the albumin fraction from 3.8 to 0.8 Gm. per hundred cubic centimeters. At the same time the serum globulin increased from a normal of 2 Gm. to 3.6 Gm. Throughout the remainder of the experiment the albumin was low and edema appeared whenever the albumin fraction fell below 0.7 Gm. per hundred cubic centimeters, independent of the total protein and globulin levels.

meters. After the animals had reached this depleted state, slight generalized subcutaneous pitting edema appeared. With the omission of plasmapheresis for even one or two days, this promptly disappeared. With the resumption of the process, the picture could be changed in from twenty-four to forty-eight hours from that of an edema-free animal to one with marked generalized anasarca. Since the shift of the edema

depended on the volume and frequency of the plasmapheresis, the dogs were carried repeatedly from the edema-free into the edematous state, and parallel determinations on the total protein, serum albumin and globulin fractions were made. These showed that, in spite of the large removal of the total proteins, the globulin fraction showed a definite increase, while the albumin fraction fell in direct proportion to the volume and frequency of the plasmapheresis. The most constant and striking observation, however, was that whenever the albumin fraction fell below 0.8 Gm. per hundred cubic centimeters, edema appeared. The lowest serum albumin observation was 0.41 Gm. per hundred cubic

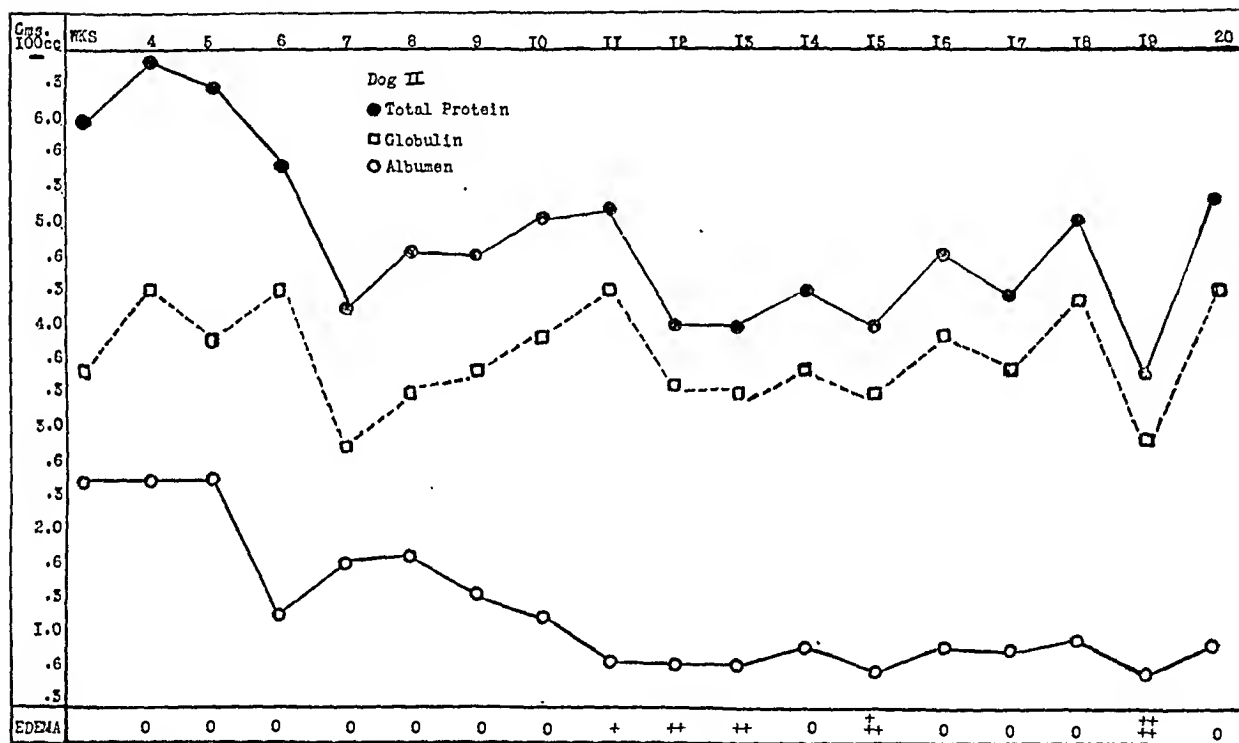


Fig. 2 (dog 2).—Chart illustrating the levels of total protein, globulin and albumin fractions in relation to edema during the course of plasmapheresis. Notice the constant association of the albumin level to edema occurring independently of the total protein and serum globulin.

centimeters. A reading of 0.6 Gm. per hundred cubic centimeters or less was always associated with ascites, pleural effusion, edema of the legs, prepuce and scrotum. All of this disappeared promptly when the albumin level rose above 1 Gm. per hundred cubic centimeters. This is well shown by the graphs on dogs 1 and 2 (figs. 1 and 2). These also indicate that edema occurred independent of the level of the globulin fraction and that the appearance of the edema was closely associated with the level of the albumin fraction. It was impossible to foretell the time of appearance and amount of edema by the total

protein level. It seemed, therefore, that, if only one blood determination was to be made, the albumin fraction was the informative one, and we soon came to look on it as the edema indicator. We spoke of this constant association of edema and the hypo-albuminemia of 0.8 Gm. as the "edema level."

A marked individual ability to stand plasmapheresis is indicated by the results obtained in this group of animals. Dog 2 was bled repeatedly, 900 cc. being drawn twice daily without the appearance of symptoms of hemorrhage or shock, while dog 3, even though much larger, was unable to stand an arteriosection of from 675 to 800 cc. without severe symptoms of hemorrhage. Similarly dog 4 showed evidence of collapse when from 400 to 675 cc. of blood was withdrawn, and he developed edema in five days following plasmapheresis. Evidence of damage to the kidney as indicated by a pathologic urinary sediment and albuminuria likewise appeared early in the latter two dogs. Our observations show that a complete recovery of the serum protein picture takes a matter of time somewhat in proportion to the severity and duration of the low proteinemia. At the beginning of the process, a return to normal took place within a few hours, but if the animal were carried to a more depleted state, a slower recovery followed. This was illustrated by dog 3. He was kept edematous for a period of one month and then allowed to recover. From the laboratory point of view and from the appearance of the dog, a complete recovery had taken place in four weeks (fig. 3).

In patients, we believe that albuminuria plays an extremely important rôle in the chronic edema of renal origin. We feel that the excessive loss of albumin in the urine in certain cases of nephritis in man stands in relation to low proteinemia and edema in man in a manner comparable to plasmapheresis and the formation of edema in our animals. In the one, the loss of serum protein is through the kidney, while in the other a loss occurred through active extraction from a peripheral vessel. However, the effect was similar with a comparable result so far as any experimental result may be applied to man.

A review of the cases of chronic nephritis with edema which have been admitted to the hospital and clinic during the past fifteen years shows that the albumin in the urine was frequently large in amount. In all of the cases that we have personally studied (twenty-seven) the loss of albumin in the urine has ranged from 5 to 60 Gm. per day. The greater the albuminuria, the more massive and more obstinate has been the edema. There is much evidence that the albumin, whether it is normal or abnormal, must come through the kidneys from the blood stream. Furthermore, if the loss is large enough, there follows a low-

ering of the total serum protein, particularly of the albumin fraction.²⁰ In our patients the loss of over 4 Gm. of albumin per day has been associated with a gradual drop of the total blood protein and when the serum albumin fraction in the blood fell to about 1 Gm. per hundred cubic centimeters, edema appeared. In the cases that we have been able to follow through such changes, this process required from six to eighteen months. Patient H¹ and Sp¹ (fig. 4) were particularly instructive in this respect. Both had a mild acute nephritis which soon subsided except for a well marked albuminuria and a relatively unimportant urinary sediment. The daily average loss of albumin was 8 and 15 Gm., respectively, and blood studies in them showed a gradual decrease in the

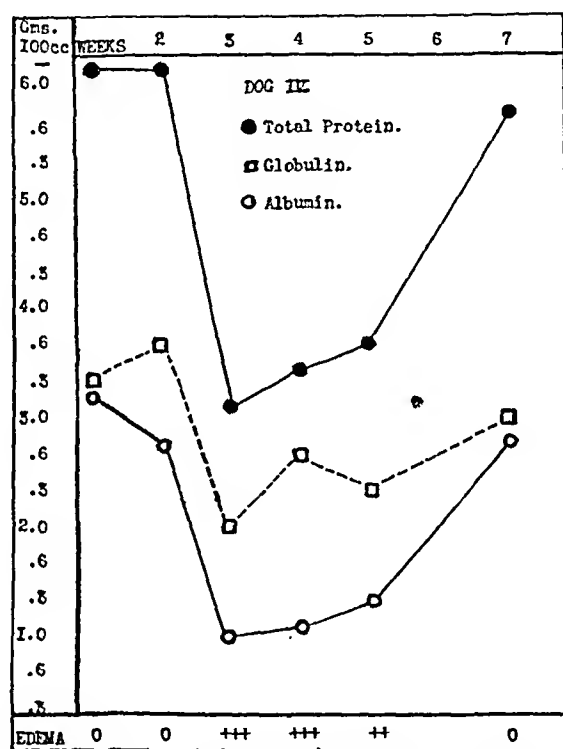


Fig. 3 (dog 4).—Chart illustrating the levels of total protein, albumin and globulin fractions in relation to edema during plasmapheresis. The first two weeks represents the period of control blood studies. On the fifth day of plasmapheresis edema occurred. The third week illustrates the low total protein and a marked fall of the albumin fraction with the occurrence of 3+ edema. Plasmapheresis was discontinued during the fourth week. The results for the fifth, sixth and seventh weeks illustrate a gradual return to normal of the total serum protein, albumin and globulin fractions.

20. Bright, Richard, quoted from Linder, Lundsgaard and Van Slyke, J. Exper. Med. 39:887, 1924, Guys Hosp. Rep. 1:848, 1836. Kisch, Franz: Eiweisskonzentration und Chlornatrium-Absorptionsvermögen des blutserums Odematoser, Klin. Wchnschr. 1:848, 1922. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. 39:887, 1924. Kollert, V., and Starlinger, W.: Ueber das Verteilungsverhältnis der Eiweisskörpergruppen des Blutplasmas und Harnes bei Nierenkranken, Klin. Med. 104:44, 1926.

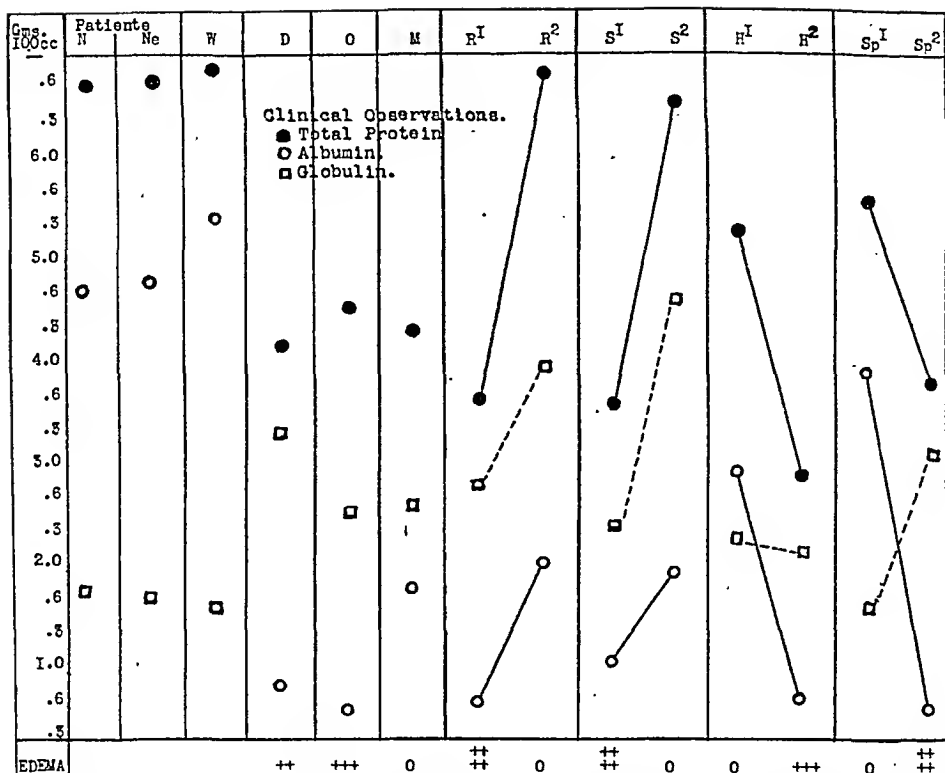


Fig. 4.—A series of cases, illustrating the levels of total serum protein, albumin and globulin fractions. *N* indicates a normal with total protein 7, albumin 5 and globulin 2 Gm. per hundred cubic centimeters; *Ne*, a case of chronic glomerular nephritis without edema showing normal levels of total protein, albumin and globulin; *W*, a case of chronic vascular nephritis with hypertension, showing normal levels of total protein, albumin and globulin; *D* and *O*, cases of chronic nephritis with edema, illustrating the typical blood observations in nephrosis. The total serum protein has dropped to 4 and 4.5 Gm. There is an increase of the globulin fraction and a profound drop of the albumin fraction with inversion of the ratio. The albumin fraction illustrates the relationship of a low albumin level to edema. *M* indicates results in a case of chronic nephritis without edema, illustrating a total protein as low as seen in the previous two cases but in which there is no edema. The albumin-globulin ratio is reversed, but the albumin fraction is not decreased to what is termed the edematous level. *R*¹ indicates results in a case of chronic nephritis with edema, illustrating the inversed albumin-globulin ratio, as low a total protein as in *M*, but in which the albumin fraction is much lower. This illustrates the relationship of a low albumin fraction to edema. *R*² is for the same case illustrating the return of total protein to a high normal level on a high protein feeding. The albumin-globulin ratio is still reversed, but the albumin fraction has become elevated so that the patient is edema-free. *S*¹ indicates a typical case of nephrosis. There is no antecedent history of acute nephritis. The total protein is markedly below normal, the albumin-globulin ratio is reversed. The albumin fraction is markedly decreased, and there is a generalized anasarca. *S*² is for the same case illustrating the results of a high protein diet. *H*¹ and *Sp*¹ show the results in cases of acute nephritis. *H*² and *Sp*² are for the same cases after from six to eighteen months of a marked albuminuria in which the patients developed changes typical of nephrosis. There is a profound drop in the total protein, the albumin-globulin ratio is reversed, but the albumin fraction dropped below 1 Gm. per hundred cubic centimeters with the formation of edema. (It is interesting to note that if lines were drawn to connect the total protein, albumin and globulin fractions of these cases that a chart would result that is similar to figures 1 and 2 of dogs 1 and 4, respectively.)

total protein with an inversion of the albumin to globulin ration (H^2 and Sp^2 , fig. 4). Finally after eighteen and six months, respectively, their serum albumin fractions had fallen well below 1 Gm. per hundred cubic centimeters with the appearance of marked generalized anasarca together with all of the observations regarded as characteristic of nephrosis.

It was of interest to be able to estimate the presence of and the amount of the edema in any renal patient by the determination of the serum albumin in a given specimen. Edema appeared at about 1 Gm. per hundred cubic centimeters of blood and increased rapidly as the albumin fraction decreased so that 0.5 Gm. per hundred cubic centimeters of blood was always associated with marked generalized anasarca, ascites and pleural effusion. Conversely, edema decreased shortly after the albumin fraction increased above 1 Gm. level. Cases B^1 and S^1 (fig. 4), illustrate this point and show the occasional improvement following dietary therapy. These patients were admitted to the hospital showing pallor, weakness, muscular wasting, marked anasarca, ascites, pleural effusion and albuminuria similar to cases D and O (fig. 4). The blood serum pictures were characteristic, and the patients were in negative nitrogen balance, as many of these cases were found to be, particularly if they have been restricted in their protein intake. On a liberal diet, high in protein, nitrogen began to be stored in quantities varying from 8 to 24 Gm. per day, and they soon passed into nitrogen equilibrium. At the same time there was a gradual increase in the serum albumin and serum globulin (B^2 and S^2 , fig. 4). Edema disappeared rather quickly, and the patients rapidly gained weight and strength and were able to go about their usual work. A comparative study of figures 1, 2 and 4 will show these clinical and experimental observations to be remarkably parallel.

The formation of the serum protein is of great interest and indicates the danger of the constant loss of albumin in even relatively small amounts. The daily average loss of globulin in dogs 3 and 2 was 10.8 Gm., while the average loss of albumin was 4.3 Gm. per day (computed by determining the albumin and globulin content of the serum discarded at each time of plasmapheresis). The globulin showed a great increase during the continued plasmapheresis, while the albumin remained at a low level. This probably indicates a rapid regenerative power on the part of the body to form serum globulin, while the serum albumin is replaced much less readily. It is not surprising, therefore, that any patient who is losing over 15 Gm. of albumin in the urine per day loses ground rapidly. At first glance the repeated extraction of so much serum from our dogs may appear to be extreme and not at all comparable to what occurs in man. A slight calculation, however, will

show that what we did to our dogs is mild in comparison to what happens in the patients with nephrosis. The dogs lost only 15.1 Gm. of albumin and globulin on the days of plasmapheresis, whereas the patients lost from 15 to 20 Gm. per day of albumin (albumin and globulin) in the urine. The amount of urinary globulin is usually small.²¹ A patient losing from 15 to 20 Gm. of albumin (albumin and globulin) per day is suffering a relative loss which is from two to three times greater than in our dogs.

The marked variation in the amount of albumin (albumin and globulin) lost by each patient (5 to 60 Gm. per day), together with the apparent individual ability both to withstand and to replace the loss of protein, explains in part the frequent failure of a high protein diet to supply the deficiency. Roughly, those patients losing under 10 Gm. of albumin and globulin per day have shown remarkable benefit from the taking of a liberal diet high in protein. Just what effect this improvement will have on the pathologic process only time will tell. However, those patients losing over 20 Gm. in the urine have rapidly progressed into renal insufficiency in spite of anything we have been able to do.

There has been considerable controversy concerning the basal metabolism in relation to nephrosis. Most authors have reported a low metabolism in patients, and many have seen good results from the administration of thyroid, such as elevation of metabolism and loss of edema. Metabolic studies were made on the dogs as described in the foregoing. In general there was a marked fall in the metabolic rate after the second or third week of plasmapheresis. The lowered metabolism occurred as the total serum protein began to fall; and this happened before the appearance of edema or changes in the urine. When the dogs were in a condition of generalized anasarca with pleural effusion, the metabolism estimates were unsatisfactory due to the dyspnea and restlessness.

The basal metabolic studies on dog 1 showed a gradual fall from 190 to 140 calories per kilogram hour. This represented the second stage of study up to the time of nephrectomy. After nephrectomy the basal metabolic rate returned to 155 calories from which level the rate gradually fell to 115 when plasmapheresis was resumed (fig. 5).

Dog 2 after the second week of metabolic studies showed a gradual fall from 160 calories to a low level of 120 (fig. 5).

The metabolic studies made on dog 4 during the first two weeks revealed a normal basal metabolic rate of 250 calories per kilogram hour. One week after plasmapheresis, the metabolic rate had dropped to a level of 230 calories. At the end of the period of plasmapheresis, the

21. Hiller, Alma; McIntosh, J. F., and Van Slyke, D. D.: The Excretion of Albumin and Globulin in Nephritis, *J. Clin. Investigation* 4:235 (June) 1927.

metabolic rate showed a definite further fall to 193 calories. From this time until the autopsy was performed, the removal of blood was omitted, and the dog was allowed to rest. The basal metabolism at the end of this rest period had returned to the normal rate of 250 (fig. 5).

The majority of our patients had a decreased basal metabolic rate varying from 0 to -35 , and was lowest when edema was the greatest. The mere presence of edema, increased weight and body surface seemed not to be entirely responsible for the fall in the metabolic rate. Zero readings were observed in an occasional patient with moderate generalized anasarca. Conversely, metabolic determinations of from -25 to -35 during the acute stage of edema were observed which shifted

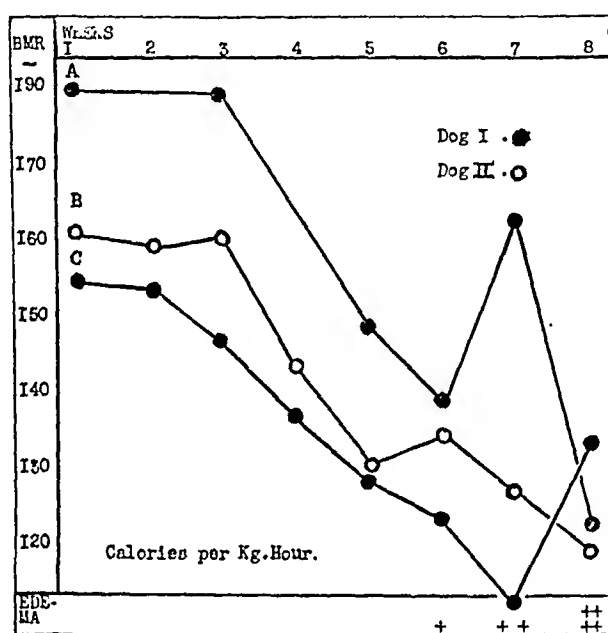


Fig. 5.—Illustration of basal metabolic studies. *A* represents the basal metabolism of dog 1 during the first period of plasmapheresis up to nephrectomy. Following this there was a postoperative rise to 165 which subsequently dropped to 120 calories per kilogram hour. *C* represents the return of the basal metabolism to 155 calories during the four weeks of convalescence. Plasmapheresis was resumed and there was a second gradual decrease of the metabolic rate to 108. *B* is the curve for dog 2 illustrating the gradual decrease of the basal metabolism from 160 to 120 calories per kilogram hour. The gradual and marked fall of the basal metabolism of the dogs during plasmapheresis was parallel with the gradual serum depletion, and occurred before the appearance of edema and urinary changes.

only slightly (from -20 to -25) after the patient became edema-free. Regardless of this lowered metabolism, most of our patients showed no improvement under thyroid therapy with doses varying from 1 to 50 grains per day. Occasionally, there was a mild diuresis with a transient loss of some of the edema.

The observations made of metabolism, in the patients and dogs, suggest that the lowered basal metabolic rate may be only a protective measure. An abnormal body metabolism may have resulted and may be a primary factor in the production of the experimental and clinical pathologic observations. In view of a lack of pathologic changes in the thyroids of our dogs, we are not justified at this time in saying more than that the lowered basal metabolic rate is probably only a protective mechanism as seen in inanition and starvation.

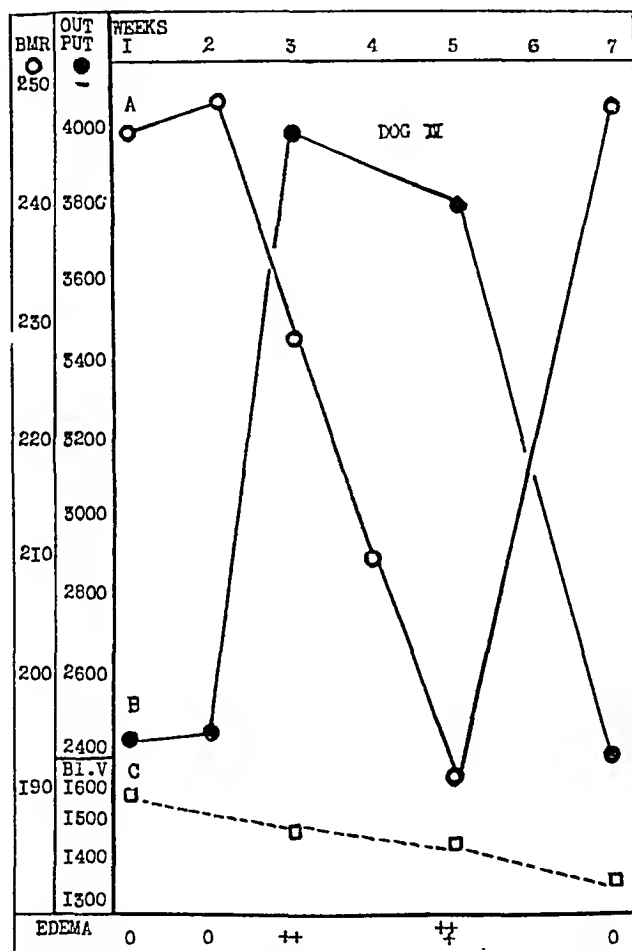


Fig. 6 (dog 4).—*A* indicates the basal metabolic rate; *B*, the cardiac output, and *C*, the blood volume. The profound drop of the metabolic rate, the marked increase of the cardiac output and the relative constancy of the blood volume during the period of plasmapheresis as shown in figure 3 are illustrated. There is a return of the metabolic rate and cardiac output to the normal during the rest period.

There is a general opinion that the blood volume does not change in cases of nephrosis and that if changes do occur, it is only in the severely anemic patients.²² Others have referred to nephrosis as a hyemic type

22. Brown, G. E., and Rowntree, L. G.: Blood Volume in Glomerular Nephritis and Nephrosi, *Arch. Int. Med.* 14:44 (Jan.) 1928.

of nephritis, suggesting an increase of the blood volume²³ (27). Figures 6 and 7 illustrate the blood volume in our dogs during plasmapheresis. These experimental studies confirm the general opinion that no changes occur in the blood volume in nephrosis. Dogs 1 and 2 (fig. 7) showed no definite changes from the normal blood volume of 1,500 cc. and 1,900 cc., respectively. Dogs 4 and 5 showed essentially the same results, i. e., plasmapheresis, edema, etc., had no effect on the blood volume.

Studies of cardiac output were made in conjunction with the studies of basal metabolism and blood volume. The cardiac output depends on

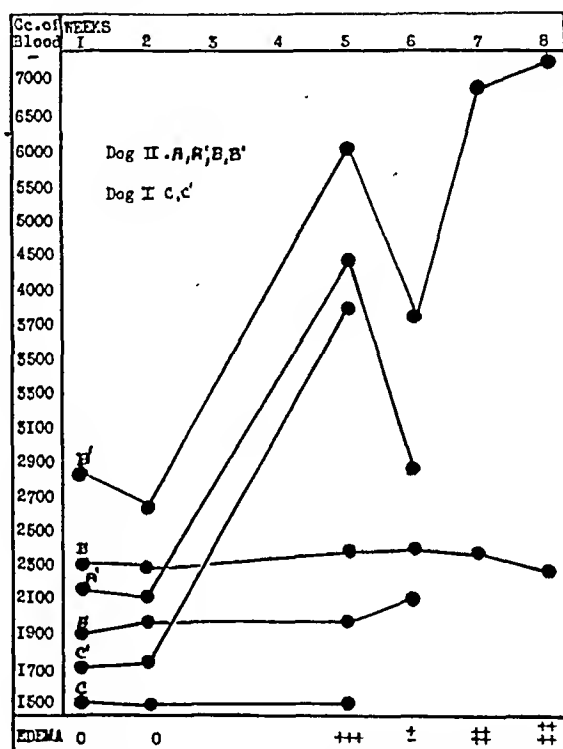


Fig. 7.—Composite chart of dogs 1 and 2 illustrating the increase of the cardiac output and the constant level of blood volume during plasmapheresis. *A* and *A'* represent the blood volume and the cardiac output of dog 2 during five weeks of bleeding followed by four weeks of rest. *B* and *B'* show the changes during a second period of plasmapheresis on dog 2. At the period of greatest edema the cardiac output increased to 7,000 and 7,800 cc. per minute. The two lines at the bottom of the chart represent the blood volume (*c*) and cardiac output (*c'*) on dog 1 during five weeks of study. These observations indicate that the cardiac output is greatly increased during periods of edema of this kind, while the blood volume is not grossly affected.

the difference of oxygen content of arterial and venous blood which was obtained from the heart. There was a definite marked increase of

23. Wright, Samson: Applied Physiology, ed. 2, Humphery Mulford, London. Oxford University Press. 1928, p. 307.

cardiac output in proportion to the amount of edema. (Figure 6 is a composite chart on dog 4, illustrating the cardiac output in comparison to changes of metabolism and blood volume. It shows the marked increase of cardiac output during the stage of edema and return to normal during the edema-free period.) Figure 7 illustrates the uniformity of change in cardiac output in different dogs under similar conditions as

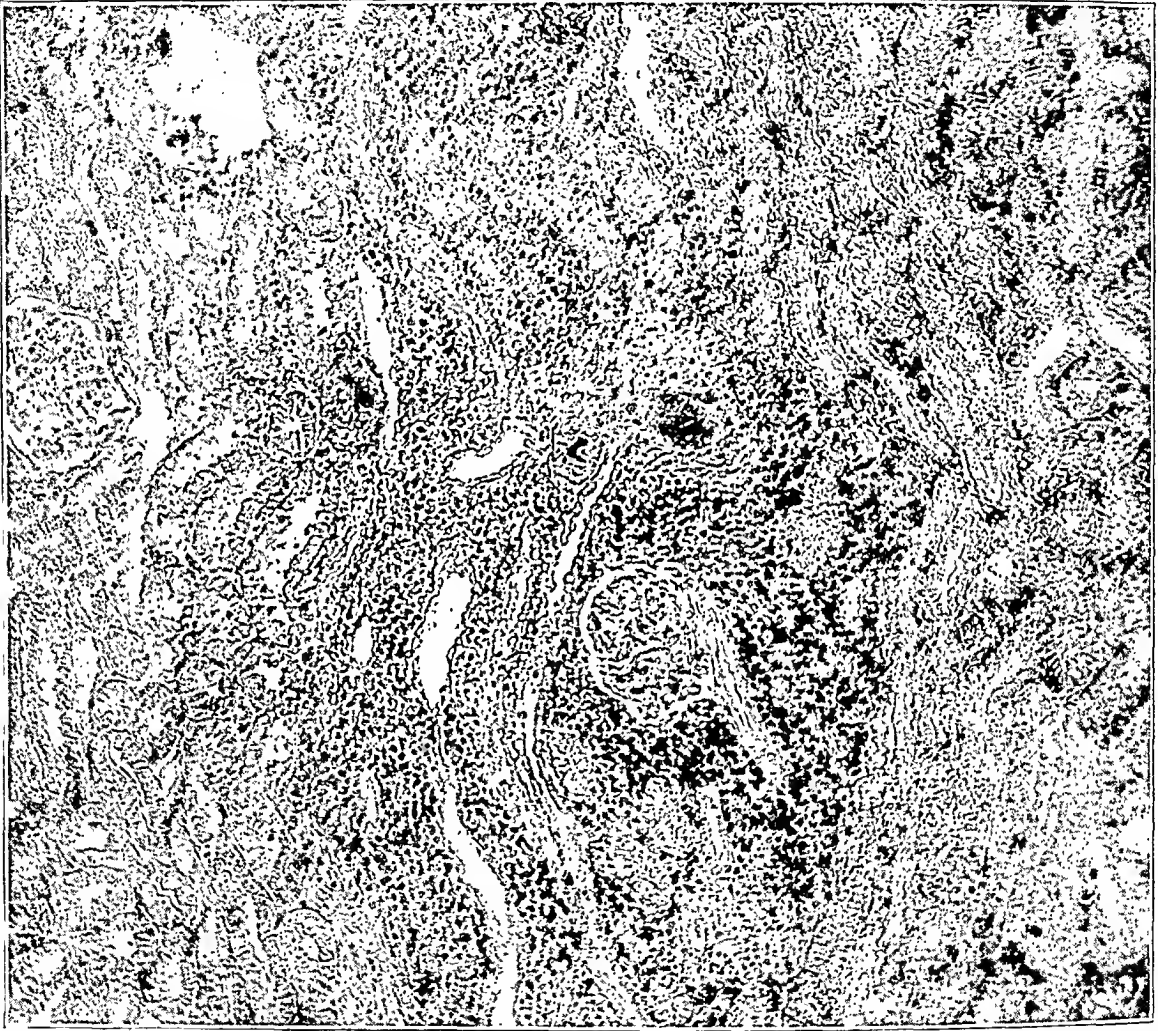


Fig. 8 (dog 1, nephrectomized kidney).—This kidney section as well as all the others was stained with eosin and methylene blue, except the last section (fig. 13), which was stained with scharlach R and slightly counterstained with hematoxylin. The microscopic study of the kidney of dog 1 illustrates moderate degree of swelling and desquamation of the tubular epithelium, definite areas of plasma cell infiltration and a rare glomerulus that shows hyalinization of Bowen's capsule. The tubules in areas of plasma cell infiltration are markedly damaged. Magnification, $\times 1565$.

produced by plasmapheresis. In dog 1 (fig. 7) the normal cardiac output was 1,700 cc. per minute. At the time of marked edema, the cardiac output rose to 3,800 cc. per minute. In dog 2, the normal cardiac out-

put was 2,200 cc. which rose to 4,500 cc. and dropped as the edema decreased to 2,900 cc. As the edema reformed, the cardiac output rose to 6,000 cc. of blood per minute (fig. 7). As massive edema was produced, the cardiac output increased markedly to 7,000 and to 7,800 cc. per minute.

The physiologic significance of such increased cardiac output in relation to edema is rather difficult to explain. It may be the result of a

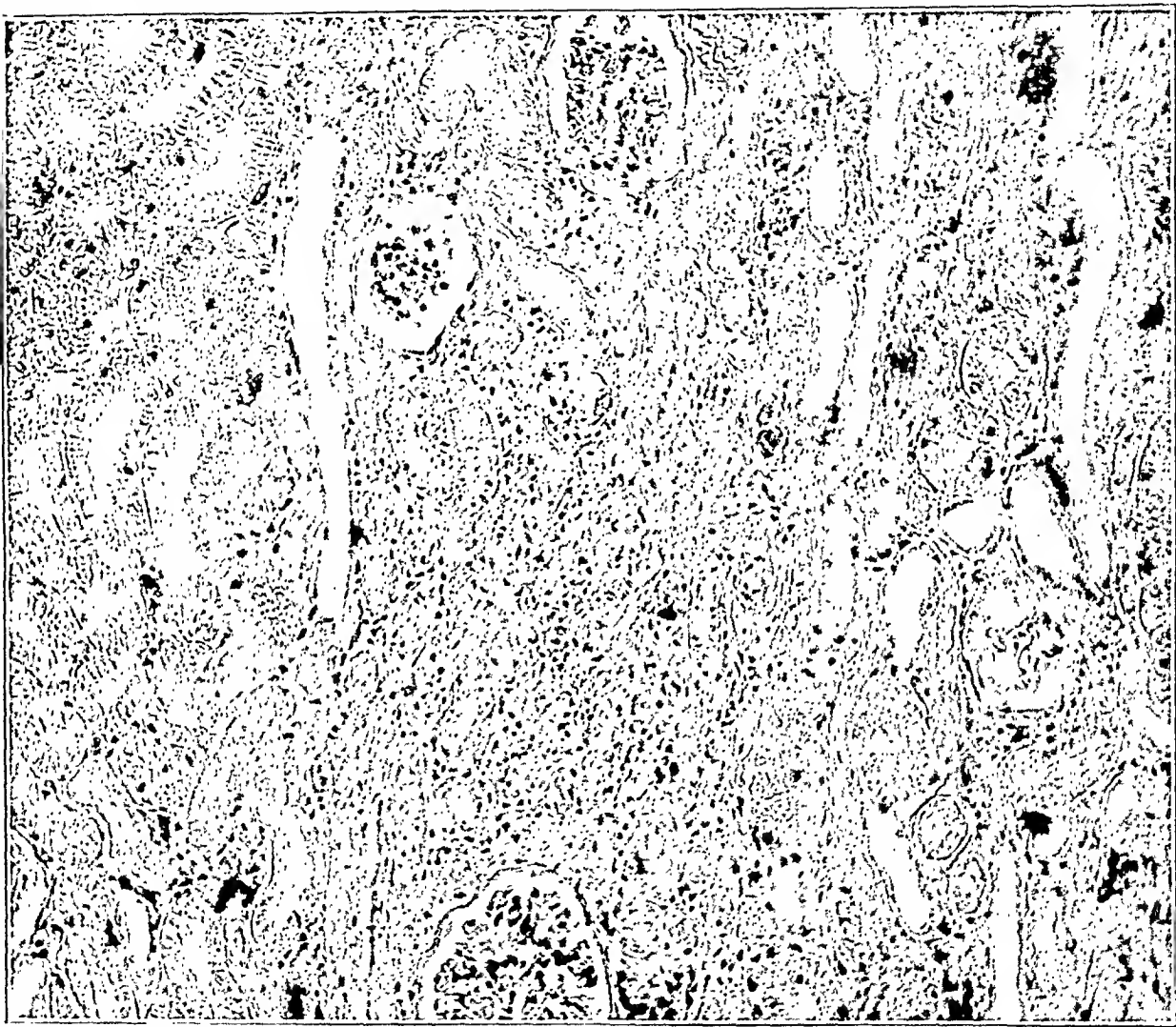


Fig. 9 (dog 1, autopsied kidney).—This section demonstrates marked progression of renal pathologic changes. Disintegration and atrophy of tubular epithelium are markedly increased. There are numerous areas of lymphoid and plasma cell infiltration and definite connective tissue replacement. Many glomeruli show thickening and hyalinization of the capsule with more glomerular atrophy than was seen previously. Magnification, $\times 1758$.

general change that is occurring in the body tissues in which there is a definite oxygen want. It may be due to the tissue demands for more nourishment, as there is a markedly low proteinemia during the greatest changes in the cardiac output. However, the oxygen carrying capacity

of the red blood cells may have been altered so that the increase of cardiac output obtained may not be an actual one.

The cholesterol, phosphorus and calcium changes in the blood are considered typical of nephrosis. Their determinations are of diagnostic interest and therefore were studied in our dogs during plasmapheresis. The cholesterol increased to as high as 254 mg. per hundred cubic centimeters. In patients with nephrosis observations of cholesterol

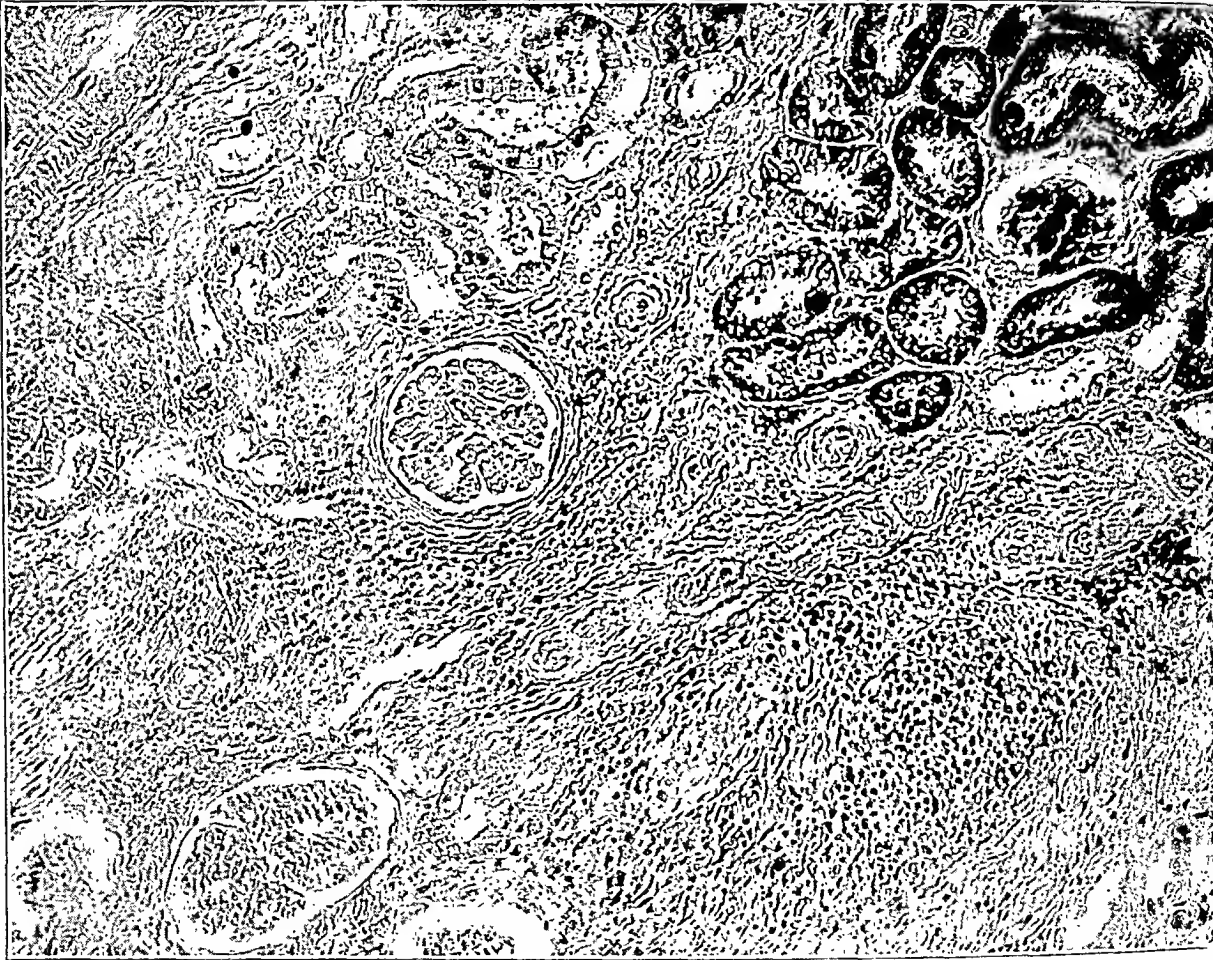


Fig. 10 (dog 2).—This kidney section shows that the predominating lesion is in the tubular region. The tubular epithelium shows marked cloudy swelling and desquamation. Definite areas of plasma and lymphoid cells accompanying areas of scar tissue replacement throughout the tubular region are demonstrated. Rather frequently atrophied glomeruli with marked thickening of the capsule can be seen. Magnification, $\times 1635$.

determinations always showed an increase. This varied from 300 to 800 mg. Phosphorus in our dogs increased from a normal of 4 and 4.5 mg. to as high as 24 mg. This was comparable to the determinations made in our patients. The calcium determinations in the dogs showed a decrease from 10.25 to 9.25 mg. per hundred cubic centimeters. In

patients with nephrosis the calcium was frequently observed as low as 8.25 mg. Efforts to maintain normal calcium metabolism in our patients by the administration of calcium or parathyroid extract were of no avail. Fibrinogen determinations were made on the dogs and showed an increase in the edematous stages to as high as 1.2 Gm. per hundred cubic centimeters of blood serum. The patients with marked edema showed a similar increase in fibrinogen from 10 to 300 per cent.



Fig. 11 (dog 3).—This kidney represents the earliest stage in the progressive lesion demonstrated in this series of animals. The tubules show cloudy swelling with slight desquamation of the epithelium in the convoluted portion. In many of the luminae can be seen hyaline and fatty casts. The glomeruli were normal except for a slight thickening of the capsule. A precipitate was seen in the capsular spaces (possible albumin) streaming down into the tubules. Magnification, $\times 2133$.

Urinalysis of the dogs after plasmapheresis was begun and after the appearance of edema, showed albumin, hyaline and granular casts, fat droplets, rare red and white blood cells and renal epithelial cells. The

specific gravities averaged between 1.030 and 1.040. In dogs 1, 2 and 3, as they became more and more depleted and as greater amounts of edema occurred, the urinary observations increased. Especially was this true of the granular casts. Late in the experimental studies of dogs 1 and 2, the specific gravity of the urine fell to 1.010 and the blood pressure rose from normals of 130 and 140 systolic and 80 diastolic to as high as 170 to 190 systolic and 90 to 110 diastolic. At this time, the

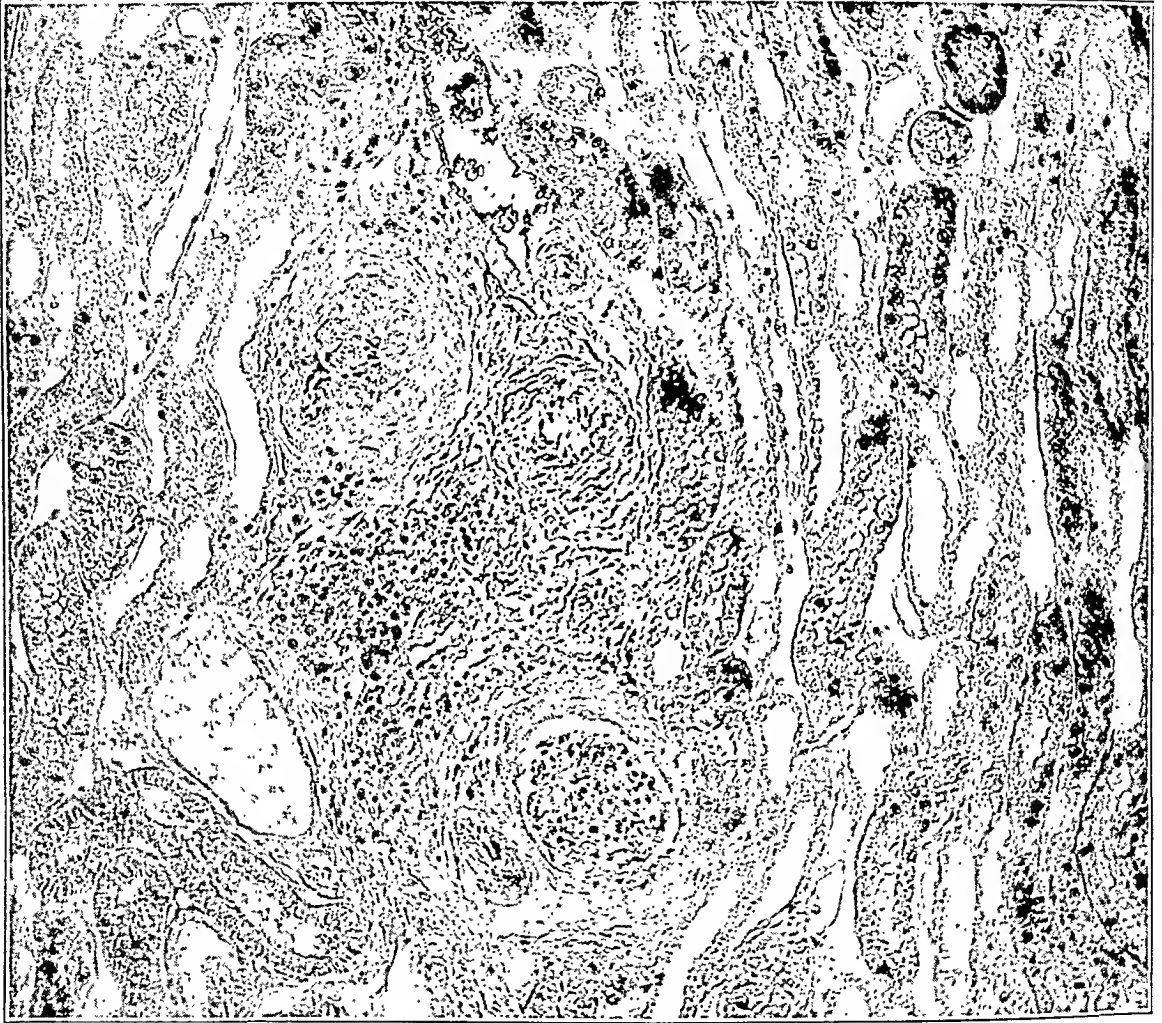


Fig. 12 (dog 4).—This kidney section demonstrates a predominating tubular lesion with a markedly swollen and desquamated epithelium. The tubules contain occasional hyaline and fatty casts. There are definite areas of small round cell infiltration accompanying a slight amount of scar tissue formation. Occasionally a glomerulus shows marked atrophy, hyalinization and thickening of the capsule. Mitotic figures were found in the tubular and glomerular epithelium. Magnification, $\times 1600$.

former amount of edema could not be maintained in dog 3 and was maintained in dog 2 only by increasing the frequency of plasmapheresis and by increasing the amounts of blood withdrawn nine fold.

The urinary and blood pressure changes as described previously served as an index of a progressive kidney damage in our dogs. The experimental results tend to support the theory that the continual loss of albumin in the urine is sufficient alone to produce renal pathologic changes. The kidneys of the dogs showed pathologic changes varying from slight cloudy swelling of the tubules, fatty, small round cell and plasma cell infiltration to marked tubular destruction, scar tissue replace-

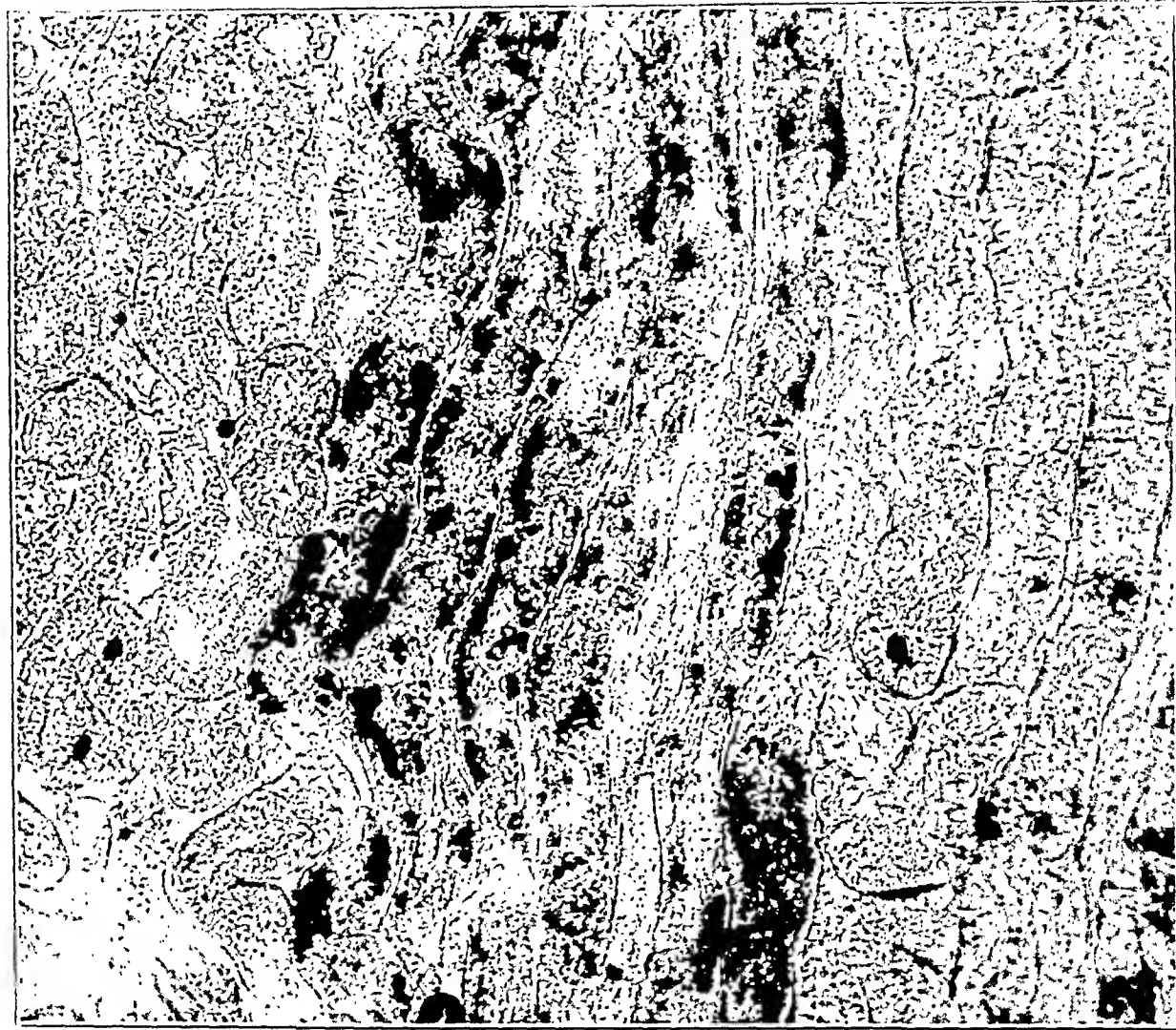


Fig. 13 (dog 4).—This kidney section (stained with scharlack R) demonstrates definitely the marked fatty infiltration or degeneration that occurred in these animals. The dark appearing stains in the tubules represent the fat. Magnification, $\times 2000$.

ment and glomerular atrophy. In the later stages the tubular atrophy, interstitial connective tissue deposits and glomerular changes were definite (figs. 8, 9, 10, 11, 12 and 13).

In our patients we feel that the early kidney change is predominantly a tubular one, and that the primary lesion was due to acute nephritis or

as in a few cases was obscured. After a variable period of time of albuminuria, the serum depletion occurred, and edema and the rest of the picture typical of nephrosis appeared. These patients usually do not die at this stage unless some severe intercurrent infection to which they are predisposed, develops. After a variable length of time of such an albuminuria, edema, etc., the blood pressure increases, the heart enlarges, changes in the eyegrounds occur, the results of renal function tests decrease, the blood urea nitrogen increases, the amount of albumin in the urine diminishes, casts and cellular elements increase, edema disappears and the disease picture gradually passes from one of tubular nephritis to one of glomerular changes; finally, the patient dies of uremia. The pathologic change in the kidney is one of a chronic mixed or diffused nephritis with marked tubular, glomerular and interstitial changes.

CONCLUSIONS

1. Edema in dogs, varying from a slight to a marked degree, can be produced by decreasing their serum protein.
2. The amount of edema both in patients and in dogs seems more closely associated with the level of the serum albumin fraction than with the total protein.
3. The basal metabolism of the dogs fell with the depletion of the blood serum.
4. The blood volume in dogs was unchanged in the edematous period, but the cardiac output was greatly increased.
5. Renal pathologic changes in dogs were produced by a low proteinemia, as shown by the appearance in the urine of albumin, granular casts, fat droplets and products of renal cell degeneration in the urine and by definite degeneration of the renal tubules, destruction of the glomeruli and scar tissue formation.

THE SEROLOGIC AND ETIOLOGIC SPECIFICITY OF THE ALPHA STREPTOCOCCUS OF GASTRIC ULCER

A BACTERIOLOGIC STUDY *

EDWARD WATTS SAUNDERS, M.D.

WITH THE TECHNICAL ASSISTANCE OF MARY A. COOPER, B.S.

NEW YORK

Because of the overwhelming trend of clinical opinion that infection is the inciting cause of gastric, duodenal and gastrojejunal ulcer, the present investigative work was undertaken by the Department of Surgical Research of Cornell University Medical College, New York City, in collaboration with the Department of Public Health and Preventive Medicine under the direct supervision of Dr. Joshua E. Sweet, Dr. John C. Torrey and Dr. Morton C. Kahn.

The work involved a bacteriologic study of gastric ulcer and the isolation of an alpha streptococcus from gastric, duodenal and gastrojejunal ulcers which is proved identical and specific by differential cultural tests and by agglutination, cross-agglutination and agglutinin absorption. The agglutinogenic and antigenic homogeneity of this type with four alpha strains, which were obtained from cases of a specific disease characterized by an acute onset of multiple typical ulcers of the lip, tongue, soft palate and pharynx, is demonstrated, and also its morphologic likeness to, but cultural and serologic difference from, all alpha strains obtained from other foci in the mouth. A comparison is also made with alpha-prime strains isolated from ulcers resulting from contact with human mouths. It is further shown that serums from patients with proved gastric, duodenal or gastrojejunal ulcer contain specific agglutinins for this alpha streptococcus type, whereas serums from patients with other streptococcal diseases fail to agglutinate it or only in low titer. Observations are also recorded as regards its pathogenic characteristics, as shown by animal inoculations. On the basis of this evidence, the theory that gastric ulcer is a specific infection is offered.

LITERATURE

Etiologic Factors Other Than Infection.—Ulcer of the stomach has been produced experimentally by many different methods, some so foreign to possible etiology in man that they will only be cited. Other

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* This report was aided by a gift from Mrs. John L. Given in support of surgical research.

methods employed have had a definite bearing on location and chronicity but probably not on etiology. Mann¹ stated that, "Chronic peptic ulcers appear to have never been consistently produced experimentally in the gastric mucosa by any method." Complete bibliographies have been compiled repeatedly, and reference may be made to those of Bolton,² Greggio,³ Ivy,⁴ Butsch,⁵ Durante,⁶ Rosenow,⁷ and recently Morton⁸ and Nickel.⁹ Nickel mentioned the following extraneous methods of production: interference with the nerve supply, section of the spinal cord, section or stimulation of the vagus or sympathetic nerves, injury of the mucosa mechanically, by excising pieces, by the use of sutures, by application of the actual cautery, silver nitrate and nitric acid, by the injection into or beneath the mucosa of such substances as foreign protein in sensitized animals, gastro-toxic serum, silver nitrate and alcohol, injection of lead chromate and fat to produce embolic lesions, by intravenous injections of poisons, such as pilocarpine, phenol, chloroform, bile salts, epinephrine, diphtheria toxin, filtrates of various bacteria and by extirpation of the suprarenal and thyroid glands, a disproportion between the gastric pepsin and the antipepsin of the blood serum, roentgen rays, spasms or portal stasis giving rise to hemorrhagic infarction and subsequent ulceration.

In 1853, Virchow initiated the idea that functional disturbances, such as hypotonia and hypertonia, have produced lessened resistance by

1. Mann, F. C., and Williamson, C. S.: The Experimental Production of Gastric Ulcer, *Ann. Surg.* **77**:409, 1923.

2. Bolton, C.: Experimental Production of Gastric Ulceration by Injection of Gastric Toxin, *Lancet* **1**:1330, 1908.

3. Greggio, Etorre: Des ulcers gastro-duodenaux, *Arch. de méd. expér. et d'anat. path.* **27**:533, 1916-1917.

4. Ivy, A. C., and Shapiro, P. F.: Experimental Production of Gastric Ulcer by Local Allergy; Preliminary Report, *J. A. M. A.* **85**:1131 (Oct. 10) 1925.

5. Butsch, J. L.: Ulcers of the Gastro-Intestinal Tract with Special Reference to Gastro-Jejunal Ulcers, Papers from the Mayo Foundation and Medical School of the University of Minnesota **1**:57, 1915-1920.

6. Durante, L.: The Trophic Element in the Origin of Gastric Ulcer, *Surg. Gynec. Obst.* **22**:399, 1916.

7. Rosenow, E. C.: The Production of Ulcer of the Stomach by the Injection of Streptococci, *J. A. M. A.* **61**:1947 (Nov. 29) 1913; The Causation of Gastric and Duodenal Ulcer by Streptococci, *J. Infect. Dis.* **19**:333, 1916; Specificity of Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization, *ibid.* **33**:248, 1923; Transmutations within the Streptococcus Pneumococcus Group, *ibid.* **1**:14, 1914.

8. Morton, C. B.: Observations on Peptic Ulcer; A Method of Producing Chronic Gastric Ulcer; A Consideration of Etiology, *Ann. Surg.* **85**:207, 1927; Healing of Experimental Peptic Ulcer After Gastro-Enterostomy, *Ann. Surg.* **85**:230, 1927.

9. Nickel, A. C., and Hufford, A. R.: Elective Localization of Streptococci Isolated from Cases of Peptic Ulcer, *Arch. Int. Med.* **41**:210 (Feb.) 1928.

interfering with the nerve or blood supply and have resulted in ulceration by digestion. Hamburger¹⁰ stated that abrasions resulting from traumatization by food or from emboli produce acute ulceration which in the presence of hypersecretion and hyperacidity from some underlying cause, such as vagotonia or reflex pylorospasm, may produce chronic ulcers. Wilkie¹¹ stated that toxic absorption from the appendix or colon could produce an irritable condition of the autonomic nervous system with a tendency to ulcer formation. Intravenous injection of toxins isolated from animals with high intestinal obstruction and the possibility of aberrant islands of intestinal glands in the stomach and duodenum which would be digested by the acid of the stomach were suggested by Sweet¹² and his co-workers as a possible pathogenesis. The most consistent experimental observations have been those of Mann and Williamson¹ and Charles Morton.⁸ These investigators have been able to produce subacute or chronic peptic ulcer quite comparable to that found in man by devising a method to divert those secretions which neutralize the gastric juice as it leaves the stomach to another portion of the intestine removed from the point of emergence of the acid. The ulcers developed in the intestinal mucosa just adjacent to the gastric mucosa in a high percentage of cases. This type of ulcer produced by surgical duodenal drainage could then be healed by gastrojejunostomy and pyloric exclusion, which completely protected the ulcers from any exposure to acid chyme. All acute lesions produced experimentally without surgical duodenal drainage heal rapidly. Morton⁸ excised pieces of mucosa in different sites of the stomach and then instituted surgical duodenal drainage. The most chronic ulcers formed on the lesser curvature and pylorus. Healing of the ulcers ensued when measures were taken to reintroduce alkali in the region of the ulcer or when the forces of the acid ejections of the stomach were diffused or counteracted.

Durante⁶ stated that ulcer could be produced by any agent capable of damaging the sympathetic nervous system which controlled circulation, secretion and profound sensibility in the stomach on which the very life of the gastric cell may be said to depend. The theory of trophic ulcer must be taken in this sense.

Friedman¹³ stated that in the dog chronic ulcers may arise from acute ulceration if certain factors are present, namely, prolonged and

10. Hamburger, W. W.: Discussion on Experimental Studies in the Production of Chronic Gastric Ulcer, *M. Rec.* **86**:898, 1914.

11. Wilkie, D. P. D.: Observations on the Etiology and Pathology of Duodenal Ulcer, *Edinburgh M. J.* **13**:196, 1914.

12. Sweet, J. E., and others: The Pathogenesis of Peptic Ulcer, *Arch. Surg.* **6**: 837 (May) 1923.

13. Friedman, J. C.: Experimental Chronic Gastric Ulcer, *J. A. M. A.* **63**:380 (Aug. 1) 1914.

probably violent action of active gastric juice (hypersecretion and hyperperistalsis), and that some ulcers may remain unhealed if the acidity later drops to normal. Other factors, such as anemia, absence of anti-pepsin and vascular obstruction, are unnecessary suppositions. He believed that Stromyer's theory of the digestive action of the gastric juice and the progress of food particles is probably correct.

Dragstedt and Vaughn¹⁴ produced chronic ulcers by the injection of silver nitrate and laying in sutures in the mucosa. The lesions caused a hypersecretion of gastric juice and healed more rapidly under alkali therapy.

The Relation of Infection to the Formation of Gastric Ulcer.—Broussais in 1823¹⁵ and Abercrombie in 1824¹⁶ described gastric ulcers as inflammatory conditions and ulcerations of the stomach. J. Cruveilhier,¹⁷ who is recognized by the French as the first to describe this disease fully, in 1830 gave complete gross morbid pathologic descriptions of ulcer of the stomach and described their inflammatory appearance. In 1838, Albers¹⁸ described the pathology of ulcers. Ulcer was considered by Lebert¹⁹ in 1857 and by Cohn²⁰ in 1860 to occur as a part of a general pyemia by the intravenous injections of pus. Gandy²¹ stated that G. Colombo²² in 1877 showed evidence of the existence of inflammation in many ulcers of the stomach. In 1874, Böttcher²³ first reported micro-organisms found in ulcer. M. Letulle²⁴ in 1888 produced gastric ulceration by injection of *Cultures microbiennes*, probably streptococci and staphylococci. He also found colonies of micro-organisms in stained sections of ulcers. M. Gilbert,¹⁵ Claude,¹⁵ Favre,¹⁵ Hal-

14. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. 8:791 (May) 1924.

15. Quoted by Gandy.

16. Abercrombie: Inflammatory Affections and Ulceration of the Stomach, Edinburgh M. & S. J. 21:1 (Jan.) 1824.

17. Cruveilhier, J.: De l'ulcère simple, chronique de l'estomac, Atlas d'anatomie pathologique du corps humain, 1830, no. 10; Traite d'anatomie pathologique générale, Paris, J. B. Bailliere et Fils, 1864.

18. Albers, J. H. F.: Beobachtungen auf dem Gebiete der Pathologie und pathologischen Anatomie, Bonn, 1838.

19. Lebert: Traité d'anat. path. 1:537, 1857.

20. Cohn: Klinik der embolischen Gefässkrankheiten, 1860, p. 523; quoted by Rosenow.

21. Gandy, Charles: L'ulcères gastrique, Thesis de la Faculté de Médecine, Paris, 1899, vol. 21; Paris, G. Steinheit, 1899, no. 592, p. 276.

22. Colombo, G.: Patogenesi dell'ulcera cronica o perforante dello stomaco, Annali universali di medicina e chirurgia, 1877, p. 239.

23. Böttcher, H.: Zur Genese des perforierten Magengeschwürs, Dorpat. med. Ztschr. 5:148, 1874.

24. Letulle, M.: Origine infectieuse de certains ulcères simples de l'estomac ou du duodenum, Bull. et mém. Soc. méd. d. hôp. de Paris 5:360, 1888.

lion,¹⁵ Wurtz¹⁵ and Charrin¹⁵ all obtained lesions in the stomach by the experimental injection of different organisms and toxins of organisms, *B. pyocyaneus*, diphtheria bacillus and *B. coli*. In 1894, Favre¹⁵ produced ulcers in the stomachs of animals by the intravenous injection of a blood culture of a patient dying in eclampsia and with erosions and ulcerations of the stomach. Gaillard,²⁵ in 1882, described micro-organisms in the tissue of ulcers. Sydney Martin,¹⁵ in 1895, stated that lesions of the stomach were identical "avec la necrose bacterienne." In 1898, Henkel¹⁵ stated that a case of ulcer of the stomach was due to a streptococcus found in the border of this ulcer. From 1880 to 1890, Gaillard,²⁵ Letulle,²⁴ Widal,¹⁵ Gandy²¹ and Dieulafoy¹⁵ endeavored, by citing observations and by experimental work, to show that simple ulcer was infectious in origin. These workers isolated a streptococcus three times, but with fresh cultures they were not able to produce the lesion in the rabbit. In 1899, Bezancon and Griffon²⁶ reported the production of ulcers in the rabbit's stomach by the injection of pneumococci. In 1901, Gordon²⁷ advocated infection as the cause of gastric ulcer and supported his claim with photomicrographs showing micrococci and chronic inflammation in ulcers. He believed the course to be bacterial necrosis, the necrosing area dropping out and being followed by further necrosis as a result of acid, leaving a punched-out ulcer. Dudgeon and Sargeant,²⁸ in 1905, isolated a diplostreptococcus from four out of nine cases of peritonitis following perforated gastric ulcer. The same organism was found in sections from the edge of the ulcer. They stated that it sometimes grew in chains. In 1906, Turck²⁹ claimed to have produced ulcers by feeding *B. coli communis* for a varying length of time to dogs. In 1913, Bolton³⁰ stated that probably the commonest cause of necrosis of the mucous membrane and resulting ulcer of the stomach is bacterial infection, that the infection occurs through the blood stream and that the necrosis is due to the direct effect on the tissues of the bacterial poison alone or together with the gastric juice.

Rosenow's⁷ first report appeared in 1913, when he claimed that streptococci quite irrespective of their original source, when of a certain grade of virulence, exhibited affinity for the gastric mucous membrane, producing a localized infection and ulcer. He believed that the organisms were carried by the blood stream, not ingested. In 1915, Rosenow and

25. Gaillard, S.: Essai sur la pathogenie de l'ulcère simple de l'estomac, Thèse, Arch. gén. de méd. 7:205 (Aug.) 1882.

26. Bezancon and Griffon: Bull. et mém. Soc. anat. de Paris 1:409, 1899.

27. Gordon, W.: The Origin of Gastric Ulcer, Bristol M.-Chir. J. 19:100, 1901.

28. Dudgeon and Sargeant: The Bacteriology of Peritonitis, London, Archibald Constable, Lt., 1905, p. 58.

29. Turck, F. B.: Ulcer of the Stomach, J. A. M. A. 46:1753 (June 9) 1906.

30. Bolton, Charles: Ulcer of the Stomach, London, Arnold, 1913, p. 396.

Sanford⁷ made cultures from the wall of ulcers in twenty-four cases. Streptococci were isolated in pure culture from nine and in mixed culture from all of the rest, nonhemolyzing staphylococci from ten cases and *Bacillus welchii* and *B. coli* in some. Four adjacent lymph glands yielded streptococci in pure culture. These authors stated that the strain from twenty-seven cases, all of chronic ulcer, produced relatively short chains and diplococci and a diffuse turbidity with much acid in dextrose and ascites broth. All streptococci from relatively acute ulcers produced typical green colonies on blood plates and usually long chains in dextrose broth. Streptococci were never grown from the normal stomach wall. In 1916, Rosenow⁷ reported that streptococci had been demonstrated in the tissue or isolated in pure culture from forty-two of fifty-four typical chronic ulcers in man. From a careful review of the article, it appears that the streptococcus was isolated six times and demonstrated in the tissue thirty-six times, as information in regard to culture was supplied in only six cases. The description of the organism states that it produced small, moist, nonadherent, discrete, grayish colonies on blood plates and short chains and masses of coccus-like forms, a diffuse turbidity with a flocculent sediment and much acid in dextrose ascites broth. It acidified but did not coagulate milk. It was not encapsulated and was bile insoluble. Rosenow stated that it resembles closely the organisms isolated from appendicitis and cholecystitis. His first cultures looked like staphylococci; there were no chains, and animal passage increased the size of the colonies and green production. There was no effect on mice following intraperitoneal injection. He found their fermentative powers extremely different, all fermenting dextrose, sucrose in fourteen of twenty strains, raffinose in eight out of fifty-two, mannitol in thirty-four of sixty, salicin in forty-six of fifty-five and inulin in three of sixty-four. He stated that the strains were not sufficiently alike to warrant considering them a distinct or specific species. A number of these cultures, however, were obtained from different sources than gastric ulcer. To produce ulceration in the duodenum of rabbits, Rosenow stated that, because of the low virulence of the strains, the intravenous dose was relatively large, consisting in the main of the growth of from 5 to 25 cc. of the broth culture per kilogram of weight. In special instances, much smaller doses sufficed to produce ulcer. Also, the selective affinity for the stomach and duodenum disappeared both after cultivation of the bacteria on artificial mediums for from one to six weeks and after animal passage, the incidence dropping from 60 to 0 per cent after cultivation and to 33 per cent after animal passage. Either or both hemorrhage and ulcer of the stomach or of the duodenum followed injection of all the strains from ulcer in a total of ninety-three animals, or 83 per cent. Either or both hemorrhage and ulcer followed injection of strains of streptococci

from sources other than ulcer in a total of ninety-nine animals, or 26 per cent. Rosenow sectioned the ulcers produced in dogs by Mann by the method of surgical duodenal drainage and found evidence of an infective process and the typical streptococcus. A culture of fresh tissue of one of the ulcers yielded a streptococcus which produced acute gastric and duodenal hemorrhages and ulcers in a high percentage of rabbits receiving injections, and few or no lesions elsewhere. In one of Durante's⁶ chronic ulcers produced by ligating the splanchnic nerves, he also demonstrated not less than fifty cocci and diplococci in the depths of the tissues which showed leukocytic infiltration. A healed ulcer from the same stomach proved to be sterile, and tissue sections showed no evidence of leukocytic infiltration.

In 1909, Helmholz³¹ reported twelve cases of duodenal ulcer in infants, aged from 1 to 6 months, which occurred during the last four months of 1908. In the first eight months of 1908 and the entire year of 1909, no further cases were observed by him. In ten out of fourteen ulcers from his first series and in all eight of the last series, diplococci were found in the ulcer base of tissue sections. A green streptococcus was isolated in one case. In 1915, Helmholz³² again reported a series of eleven cases of duodenal ulcer in infants observed during the seven months from September to April. These were the only cases observed and "appeared to be an epidemic." In his series, he has demonstrated streptococci in all but four of fourteen ulcers. Rosenow was able to produce typical lesions in rabbits with the only strain isolated by Helmholz, and believed the organism identical to those he, Rosenow, had isolated.

Holt³³ and Veeder,³⁴ in their reviews of all cases of duodenal ulcer in children, reported in the literature (about 100 in all), showed that they occur in infants aged from 1 to 6 months, and only in marasmic infants with general lowered vitality.

In 1916 Celler and Thalheimer³⁵ isolated a nonhemolytic streptococcus from seven chronic ulcers removed at operation, using Rosenow's technic. The organism was described as a small gram-positive coccus forming short and long chains. The cultural characteristics of the organism were reported as almost identical with those of the strains isolated by Rosenow. With special stains, the organism was found only in or on the lining of the degenerating tissue but never in the depths. The chief organisms were minute cocci. These authors con-

31. Helmholz, H. F.: *Arch. Pediat.* **26**:661, 1909.

32. Gerdine, Linton; and Helmholz, H. F.: *Duodenal Ulcer in Infancy and Infectious Disease*, *Am. J. Dis. Child.* **10**:397 (Dec.) 1915.

33. Holt, L. E.: *Duodenal Ulcer in Infancy*, *Am. J. Dis. Child.* **6**:381 (Dec.) 1913.

34. Veeder, B. S.: *Duodenal Ulcer in Infancy*, *Am. J. M. Sc.* **148**:709, 1914.

35. Celler and Thalheimer: *J. Exper. Med.* **23**:791, 1916.

cluded that some cause is operative in certain cases, preventing the healing of defects in the gastric mucosa, and is inoperative in others. Even though a nonhemolytic streptococcus is present in practically all gastric ulcers, they did not believe that it had been proved to be a factor that either initiated ulceration or prevented healing. They were unable to reproduce the lesions in the stomachs of rabbits as Rosenow had done. They made no attempt to identify their strains serologically. In 1918, McMeans³⁶ stated that he was unable to support Rosenow⁷ in the view of elective affinity. He produced experimental bacteremia in rabbits following the intravenous injection of various organisms obtained from different sources and observed with equal frequency hemorrhages and erosions in the stomachs of rabbits inoculated in this way. The organisms used were obtained from foci of infection in patients with ulcer. In 1923, Rosenow⁷ stated that he believed the streptococcus of gastric ulcer produced a poison within its substance and free in broth cultures which injured the mucous membrane of the stomach. By immunizing one group of rabbits to ulcer strains and another group to encephalitis strains of streptococci and then making injections into all the rabbits with vulnerable doses of living ulcer-forming streptococci, he found that ulcers did not form in the animals immunized to the ulcer strains, whereas they did appear in the control rabbits immunized to encephalitis strains, but because of the disproportion of animals receiving injections (twenty-three with ulcer vaccine and seven with encephalitis vaccine) no definite conclusion should be drawn.

In 1925, Haden³⁷ made cultures from the roots of the teeth of twelve patients suffering from gastric ulcer and obtained a nonhemolytic streptococcus. Fifty-three per cent of forty-five rabbits receiving intravenous injections of broth cultures of these organisms showed gross lesions of the stomach or the duodenum, while 7 per cent of 535 rabbits receiving injections of broth cultures from 191 control patients showed similar lesions. The lesion produced was usually hemorrhagic erosion of the duodenum and occasionally, small ulcers.

In 1925, Meisser³⁸ gave eighty-one rabbits injections with the streptococcus obtained from teeth foci of twenty-two patients with ulcer and obtained hemorrhagic lesions of the stomach in 67 per cent. In 1925, Alban Girault³⁹ isolated a streptococcus from a gastric ulcer and made an emulsion (1,000 million to the cubic centimeter). This

36. McMeans, J. W.: Concerning the Gastric Lesions Observed in Experimental Bacteremia, *Arch. Int. Med.* **22**:114 (July) 1918.

37. Haden, R. L.: The Elective Localization of Bacteria in Peptic Ulcer, *Arch. Int. Med.* **35**:457 (April) 1925.

38. Meisser, J. G.: Further Studies on Elective Localization of Bacteria from Infected Teeth, *J. Am. Dental A.* **12**:554, 1925.

39. Girault, Alban: *Arch. de mal. d. l'app. digestif* **14**:924, 1924.

emulsion was used for skin sensitivity tests in patients with ulcer. It did not prove successful; so a small amount was injected deeply into the deltoid region of fourteen patients with proved gastric ulcer. Nine showed a positive reaction (tenderness, redness and swelling). Five showed a negative reaction. Duval, Roux and Moutier⁴⁰ stated that they had observed fever and leukocytosis (of 7,000, 10,000 and 32,000 cells) in twenty-eight cases of proved ulcer. They isolated a streptococcus from four of nine ulcers. Razemon⁴¹ studied thirty-one ulcers and found only six sterile lesions. Roux and Girault⁴² stated that when an ulcer is due to a streptococcus, vaccine therapy is indicated but that there is the danger of causing hemorrhage or perforation of the ulcer. They did not believe that ulcer was always due to a streptococcus, saying, "Sur un maladie à evolution aussi irregulaire que l'ulcère gastrique," and that vaccine therapy would benefit only those cases due to the streptococcus. Pierre Delbet believed that infection plays a large rôle in gastroduodenal ulcer and has successfully given a vaccine of pyocyaneus, coli, etc., to stop gastric hemorrhages. In 1925, Ivy and Shapiro⁴³ obtained necrosis, sloughing and healing of the gastric mucosa in from twenty-one to thirty days, in previously sensitized dogs following the injection of egg albumin, beef protein, etc.

In 1928, Nickel and Hufford⁴⁴ studied eighty consecutive cases of gastric ulcer, eighteen of which were of recurring and sixty-one of primary ulcer. One hundred and three strains of green-producing streptococci were obtained from various foci of the sixty-one cases of primary ulcer. Lesions of the stomach and duodenum were obtained in 63 per cent of the rabbits receiving injections of these strains. The foci included teeth, tonsils, prostate and cervix. Thirty-four strains were isolated from the foci of eighteen patients suffering with recurring ulcer, and lesions were produced in 71 per cent of the animals receiving injections. A green-producing streptococcus was isolated from ten resected gastric ulcers. In twenty-eight of thirty-one rabbits receiving injections of these ten strains, lesions resulted. Nickel stated that the green-producing streptococcus isolated was morphologically and according to sugar reactions indistinguishable from other green-producing strains which were isolated in arthritis, myositis and other conditions. He concluded that the causative streptococcus has been demonstrated in and isolated from the resected ulcer of man as well as from the

40. Duval; Roux and Moutier: *Rôle de l'infection dans l'évolution des ulcères gastroduodénaux*, *Presse méd.* **33**:3, 1925.

41. Razemon, quoted by Duval, Roux and Montier.

42. Roux and Girault: *Arch. d. mal. de l'app. digestif.* **15**:949, 1925.

43. Ivy, A. C., and Shapiro, P. F.: *Experimental Production of Gastric Ulcer by Local Allergy*, *J. A. M. A.* **85**:1131 (Oct. 10) 1925.

44. Nickel, A. C., and Hufford, A. R.: *Elective Localization of Streptococci Isolated from Cases of Peptic Ulcer*, *Arch. Int. Med.* **41**:210 (Feb.) 1928.

foci of infection and has produced electively similar lesions of the stomach and duodenum when injected intravenously in rabbits.

No cultural or serologic identity tests were attempted, without which one could not possibly conclude that the green-producing streptococcus obtained from gastric ulcer, teeth, tonsils, prostate and cervix are one and the same organism.

Nickel's technic in producing lesions in rabbits was to inject freshly isolated broth cultures, approximately eighteen to twenty-four hours old, in the marginal vein of the rabbit's ear; the dosage varied from

TABLE 1.—*Sources of Single Colony Strains from Stomach**

Patient	Hospital	Uleer	Single Colony Strains		Surgeon
1	Second Surgical, Bellevue	Large gastric, lesser curvature	1 A' 2 A	3 A 4 A	Santee
2	Second Surgical, Bellevue	Small gastric, lesser curvature	19 AA' 20 A	21 AA' 22 A	Santee
3	Second Surgical, Bellevue	Small gastric, lesser curvature	23 A 23a A	23b A 23c A 23d A 23e A	Santee
4	Second Surgical, Bellevue	Malignant ulcer, midstomach	45 A 45a A	45b A 45c A 45d A 45e A 45f A	Santee
5	Mount Sinai, no. 300520	Duodenal	46 A 46a A	45b A	Berg
6	Mount Sinai, private patient	Large gastric Lesser curvature	47a A I II	Piece from surface of ulcer 47b A I A II A III A IV A whole section V A VI A	Berg
7	Mount Sinai, no. 300534	Large gastric, lesser curvature	53 A 53a A	53b A 53c A 53d A	Berg
8	Second Surgical, Bellevue	Gastrojejunal duodenal still present; no growth	55 A 55a A	55b A 55c A 55d A	Dudley
9	Second Surgical, Bellevue	Gastrojejunal duodenal still present; no growth	56 A	56a A	Dudley
Strain from patient 2 injected into dog's stomach, strain recovered twenty-five days later			9 A 9a A	9b A 9c A	

* In this table and in the other tables, A indicates alpha; A', alpha-prime; AA', alpha-alpha-prime, and B, beta.

2 to 12 cc., depending on the size of the rabbit and the density of the culture. This injection was repeated once or twice with rapidly made subcultures, depending on the condition of the rabbit.

BACTERIOLOGIC AND SEROLOGIC REPORT

Streptococcal Types Isolated and Studied.—The sources from which the single colony strains, isolated from the multiple lesions and foci, were obtained are shown in the following tables (table 1).

There were forty-six single colony strains of streptococci isolated from nine resected gastric, duodenal and gastrojejunal ulcers cultivated immediately on resection at the operating table. Four single colony strains were recovered from the submucosa of a dog's stomach twenty-

five days after the injection of culture no. 2 into it. Forty-seven were alpha, two alpha-alpha-prime⁴⁵ and one alpha-prime strains.

Table 2 includes nineteen single colony strains which were isolated from five patients suffering from an acute disease characterized by fever and toxicity, presenting small punched out ulcers of the lip, tongue, tonsils and buccal membranes. In two patients, the condition became chronic with ulcerations of the tonsils and posterior pharynx; one

TABLE 2.—*Source of Single Colony Strains from Throat*

Patient	Ulcer	Single Colony Strains		
10	Throat.....	29 A	29b AA'	29d AA'
		29a A	29c AA'	
11	Throat.....	32 A	32b A	32d A
		32a A	32c A	
12	Lip and throat.....	37 A'	38 A	
13	Throat.....	39 A	39b B	
		39a A		
14	Throat.....	44 B	44b B	
		44a A	44c A	

TABLE 3.—*Source of Single Colony Strains from the Teeth*

Patient	Ulcer	Single Colony Strains		Teeth Foci
15	Duodenal.....	12 A		
16	Gastric.....	13 A		
17	Gastric.....	14 A		
18	Small gastric.....	15 AA'		
		16 A		
19	Small gastric.....	17 AA'		
		18 AA'		
20	Duodenal.....	28 A	28b A	
		28a A	28c G	
21	Duodenal.....	33 G	33b G	33d AA'
		33a G	33c G	
22	Duodenal.....	34 G	34b G	
		34a G		
23	Duodenal.....	35 G	35b G	
		35a G		
24	Hand—put wound to mouth repeatedly.....	27 A	27b A	
		27a A	27c A	
25	Died from Ludwig's angina.....	25 AA'	25b AA'	25d A'A
		25a AA'	25c A	

patient recovered in about two months; the other left the hospital acutely and critically ill, with beginning disease of the vocal cords and could not be followed, and in three the condition cleared up spontaneously in from ten days to two weeks. Twelve strains were alpha, three alpha-alpha-prime, one alpha-prime and three beta.

Table 3 shows thirty-one single colony strains which were isolated from foci in the teeth of nine patients suffering from gastric and duodenal ulcers, and one patient who had repeatedly put a skin wound

45. The term alpha-alpha-prime is explained later in the article.

of his hand to his mouth, thus causing an ulcer of the hand. Twelve were alpha, eight alpha-alpha-prime and eleven gamma strains. Streptococci obtained from the teeth of a patient who died with Ludwig's angina were also included in this series.

Table 4 shows eighteen single colony strains isolated from seven ulcers of the skin, lip or mouth due to traumatic injury causing the penetration of a tooth (human bite ulcers). This type of ulcer should not be confused with the human bite ulcer due to spirochetes and fusiform bacilli reported in the literature. Twelve were alpha-prime, three alpha-alpha-prime and three alpha strains.

TABLE 4.—*Source of Single Colony Strains from the Skin, Lip and Mouth*

Patient	Hospital	Ulcer	Single Colony Strains	
26	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	5 A'	6 A'
27	Second Surgical Clinic, Bellevue	Lip; tooth pierced upper lip	7 A'	8 A'
28	Second Surgical Clinic, Bellevue	Hand; put wound to mouth repeatedly	11 A'	
29	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	26 A a AA' b AA'	c A d AA'
30	Second Surgical Clinic, Bellevue	Penetration of dorsum of hand by a tooth	30 A' 30a A'	30b A'
31	Second Surgical Clinic, Bellevue	Lip; loss of lower lip by penetration of own teeth	31 A' 31a A' 31b A'	31c A'
32	Second Surgical Clinic, Bellevue	Lip; injury to lower lip	40 A	

TABLE 5.—*Miscellaneous Single Colony Strains*

Patient	Hospital		Single Colony Strains
33	Second Surgical, Bellevue	Streptococcus.....	43 B
34	Second Surgical, Bellevue	Erysipelas.....	41 B
35	Second Surgical, Bellevue	Empyema of thoracic cavity.....	42 B

Table 5 shows three single colony strains which were isolated from three patients suffering from streptococcus gangrene, erysipelas and empyema of the thoracic cavity, respectively. These three were beta strains and were used for comparative purposes.

This makes a total of 117 single colony strains of streptococci, from which the strains used for the cultural and serologic investigation were chosen. Direct smears for spirochetes, fusiform bacilli, yeast and the Klebs-Loeffler bacillus were repeatedly reported negative by more than one observer in each of the four cases reported in table 2.

In four cases of ulcer of the stomach streptococci were not recovered. Two of these were jejunal ulcers, and only the platinum loop could be pressed into the crater, a piece of tissue not being available. Three were duodenal ulcers, two in the same patient, who had had a previous

gastro-enterostomy and in whom gastrojejunal ulcers were present. The duodenal ulcers showed signs of healing but still were present. Cultures from these were sterile after ten days at incubation temperature.

A piece of duodenal mucosa from a patient operated on for ulcer but presenting duodenitis was likewise sterile. *Micrococcus gazogenes*, a minute gram-negative diplococcus, an obligatory anaerobe, was the only organism grown from a large gastric ulcer on the lesser curvature in the midportion of the stomach. This organism has been described by Hall⁴⁶ as occurring in the flora of the mouth and also by Noble. Normal mucosa of the stomach gave repeatedly sterile cultures except for one case in which a gamma enterococcus was grown. The alpha streptococcus was obtained in pure culture from five ulcers and mixed with either *B. welchii*, *B. coli*, a gamma enterococcus or a peculiar staphylococcus in four. A culture was obtained from a case of empyema of the gallbladder, one of an acute suppurative appendix and one of peritonitis, the result of a perforated duodenal ulcer of one day's duration. The alpha streptococcus was not obtained from any of these. A gamma streptococcus (enterococcus), staphylococcus and morphologically varying bacilli were the organisms recovered.

Technic.—Cultures from all ulcers of the stomach were taken in the operating room immediately on resection. Small pieces of the ulcer, about 0.25 cm. in diameter, were cut out aseptically and with a platinum loop placed into a tube containing about 15 cc. of 0.5 per cent semisolid hormone agar medium (Huntoon) with a reaction of p_H 7. When the platinum loop was heated slightly, the tissue could be readily carried to the bottom of the tube. From six to eight cultures were made from each ulcer, pieces of tissue from different areas and different depths of the ulcer being used; the pieces were washed in sterile saline solution in some cases and not in others. Cultures from pieces of normal stomach wall were made in the same manner. The first ulcer was cultivated anaerobically in a kidney and serum medium and sealed with petrolatum. It was incubated for twenty-five days before examination. A streptococcus was the only growth obtained, except for a few large gram-positive bacilli; after plating, the streptococcus colonies were transferred to the semisolid hormone agar. They grew so well in this medium that all cultures were taken directly into it thereafter. There was never any growth at the top of the stab culture unless contaminants were present. The organism grew profusely in the depth of the stabs. This method seemed simpler than Rosenow's method in which tall ascites-dextrose-agar tubes are used to obtain the right oxygen tension and was apparently as effective. At the end of twenty-four hours, there was usually no growth. The tissue would then be stirred up with a sterile platinum loop. This was repeated at the end of each twenty-four hours until growth appeared, or up to ten days if the culture remained sterile. Growth usually appeared in from three to six days. As soon as growth appeared, which was always adjacent to the tissue, it was transferred to other semisolid hormone agar tubes, incubated for twenty-four hours and then placed in the icebox. It was noted that the tubes

46. Hall, I. C.: The Anaerobic Bacteria of the Oral Cavity, Proc. Soc. Exper. Biol. & Med. 22:541, 1925.

containing the largest pieces of tissue were usually the sterile tubes. It was felt that the tissue possibly contained a bactericidal substance that prohibited growth. For this reason, small cut sections were used. Wilkie⁴⁷ found this true in cultures made from lymph glands. If contaminants appeared on the surface of the agar, the tube was cracked by filing circularly 1 cm. below the surface of the agar and applying a red hot end of a file to the groove; this would crack the tube evenly. The piece of tissue and deep solid mediums were then transferred to a sterile petri dish, and either the growth or the tissue transferred to another tube of semisolid agar. This proved to be a time-saving and efficient procedure and was devised by Dr. Kahn. The first growth in the hormone agar was immediately surface seeded on two bromcresol purple lactose agar plates. After from twenty-four to forty-eight hours' incubation at 37 C. from six to eight single, well isolated, similar streptococcal colonies were then fished into semisolid hormone agar tubes. After forty-eight hours' incubation, each culture was streaked on a plain blood agar plate (p_H 7.4) for purity of culture and effect on the medium, and the observations were recorded at the end of twenty-four hours and forty-eight hours. The plates were then left in the icebox for four or five days when the degree of hemolysis, if present, was increased. Transplants of each purified stock culture were made every three weeks, that being considered the limit of safety.

Cultures from the teeth were made directly with the platinum loop, after the mouth was cleansed, from the pockets between the teeth and the gums; the patients in every case had marked pyorrhea so that the platinum loop could be forced to the bottom of the tooth socket. These were planted directly into the semisolid agar. These tubes could be cracked in twenty-four hours, the surface growth which was always profuse, discarded, and the growth from the bottom transplanted. The growth was then carried through in the same manner as that described for the ulcer strains.

Haden,³⁷ Nickel⁹ and Meisser³⁸ obtained the streptococcus from teeth after extraction by cleansing and putting the apex of the tooth, cut off with sterile nippers, into the culture medium. By this method, a different streptococcus may possibly have been obtained.

The ulcers of the skin and lip caused by human bites always had a creeping, dissecting edge. After cleansing the surface, the platinum loop could be forced under this dissected edge. In the majority of these cases the streptococcus was the only growth, so that the tubes did not have to be cracked. The experiment was then carried on in the same manner.

Cultures were obtained from the four specific acute cases of ulcers of the lip, the tongue, the buccal membranes and the tonsils by cleansing the mouth and applying the platinum loop as in the ulcers of the skin caused by human bites. With these cultures, contaminants were rare.

For experimental inoculations into animals, the procedure consisted of direct injection into the stomach wall of twenty-four hour dextrose broth cultures (p_H 7.4). The growth was decidedly less in plain broth. For intravenous injections into rabbits, the saline washings of the twenty-four hour growth on 0.5 per cent hormone agar slant were used.

The sections cut for Levaditi stains were fixed in 10 per cent neutral solution of formaldehyde immediately on resection.

47. Wilkie, A. L.: The Bacteriology of Cholecystitis, *Brit. J. Surg.* **15**:450, 1928.

The Morphology of the Alpha Streptococcus.—The organism varied markedly, depending on its age and the mediums on which it was cultivated. The first ulcer in the stomach had been cultivated anaerobically in serum kidney broth sealed with petrolatum for three weeks. Direct smears from this growth showed short chains of diplococci. The individual diplococci appeared large and lanceolate in shape and showed many large, involuted forms. The growth on a blood plate from the original culture showed two different types of colonies, one a small discrete grayish-white colony producing a faint hemolysis, the other colony not showing any hemolysis but definite greening. On staining, both colonies appeared the same. These colonies when transferred to dextrose broth and cultivated for two or three days at incubation temperature showed a varying size of lanceolate gram-positive diplococci in short and long chains. Some appeared distinctly as rods or fused cocci resembling rods and short bacilli (fig. 1, *B*).

All of the direct original cultures on semisolid hormone agar appeared morphologically the same on first growth, that is, lanceolate cocci often fused together as short rods (fig. 1, *A*).

It would be impossible to say from the morphologic aspect alone that cocci and bacilli were not present; however, when this primary growth was passed through dextrose broth only long and short chains of lanceolate cocci would be present, varying distinctly in size and shape (fig. 1, *B*).

The first three cultures when streaked on plain meat infusion blood agar plates (p_H 7.4) were read as alpha prime streptococci after forty-eight hours at incubation temperature. However, when they were again put on these blood agar plates after artificial cultivation, there was no sign of hemolysis and only slight greening on the surface, but marked greening when the inoculated loop was penetrated into the medium. Some few colonies showed the faintest possible zone of hemolysis which would again be lost on further artificial cultivation.

After a gastric strain, culture 23, was approximately 5 months old and was in its tenth generation and had been in the icebox for ten days, a twenty-four hour dextrose broth culture was made. This culture well diluted was seeded on plain and dextrose meat infusion blood agar plates (p_H 7.4) and incubated at 37 C. A twenty-four hour reading showed equal growth on both plates of equal sized colonies about 0.5 mm. in diameter with irregular edges and a rough surface. There was markedly more greening on the dextrose blood plate, but the strain was not definitely glycophilic. A forty-eight hour reading was practically the same, except for a slight increase in size to from 0.75 to 1 mm. in diameter. The colonies were extremely adherent to the medium. This culture was also put on whey agar, p_H 5.8, on which *Streptococcus fecalis* grows well, but there was no growth of this organism in forty-eight hours.

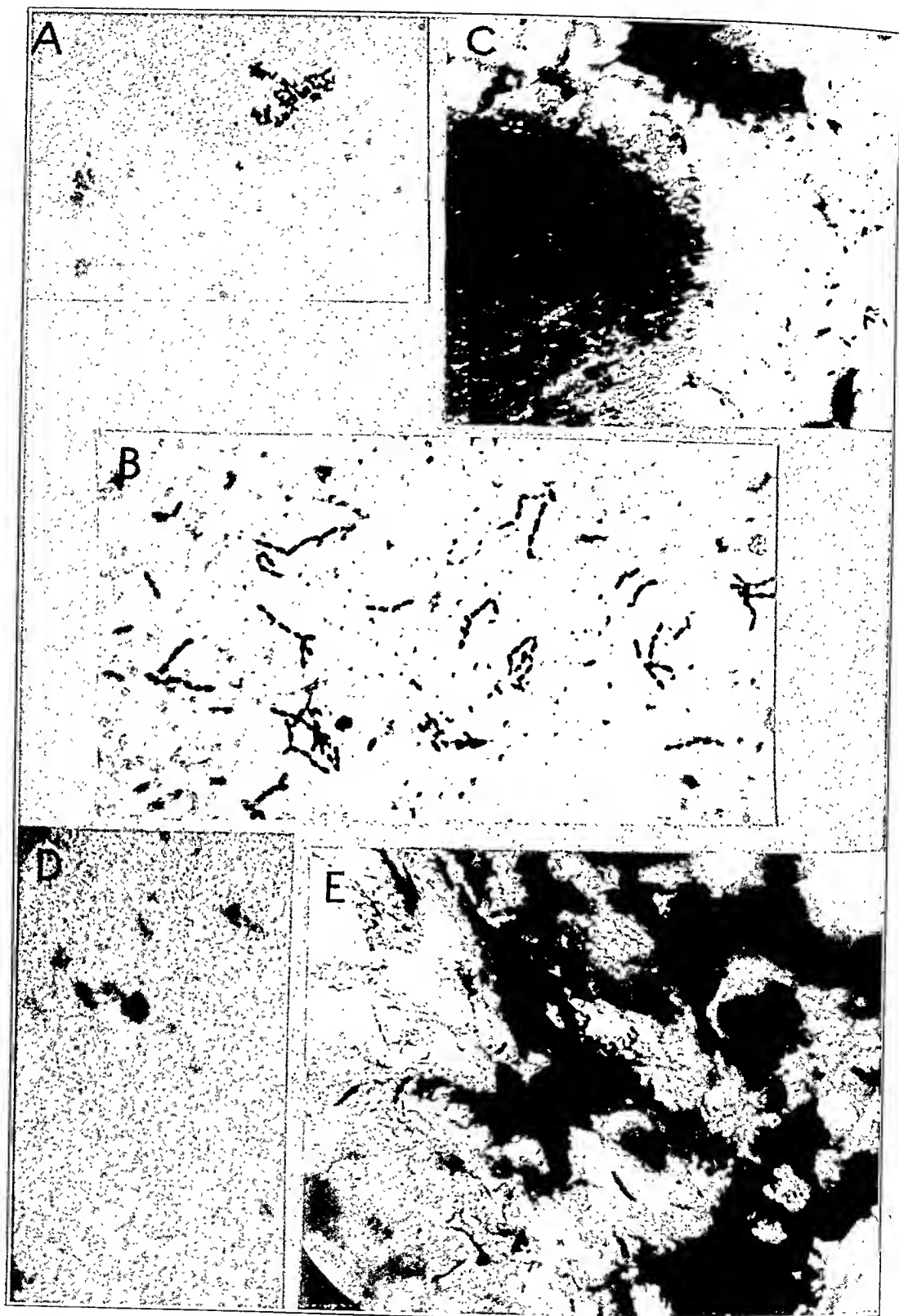


Fig. 1.—*A*, the morphologic appearance of the original growth of gastric streptococcus from ulcer tissue in 0.5 per cent hormone agar, showing no chains, but bacilloid and fused cocci forms clumped together. *B*, chaining together of lanceolate diplococci forms with some bacilloid forms after artificial cultivation. *C*, bacilloid and diplococci forms in the necrotic surface of an ulcer. Levaditi tissue section. *D*, diplococci forms in the necrotic exudate below the surface of the ulcer. Levaditi tissue section. *E*, Levaditi tissue section from a granuloma at the base of a tooth after extraction, showing many spirochetes and fusiform bacilli, but no diplococci.

Heat resistance of this culture had previously been tested when it was in its first generation along with two other cultures in their first generation, namely, 2 and 19. Twenty-four hour cultures in plain nutrient broth (p_H 7.2) were heated in narrow tubes to 60 C. for fifteen minutes and then tested for sterility by streaking on agar plates. The organisms were not killed but grew out profusely in twenty-four hours. It was again tested on the present (tenth) generation, being heated in milk tubes to 65 C. for twenty minutes, which is slightly above the heat used in pasteurization processes and which is considered sufficient to kill all nonspore-bearing pathogenic organisms within thirty minutes in commercial processes. The heated culture was then streaked on cresolpurple lactose agar plates, but there was no growth after forty-eight hours' incubation. This may be due to its slightly lowered resistance, the result of artificial cultivation. The organism grew slightly more profusely in dextrose broth than in plain broth. The growth in semisolid hormone agar stabs was profuse, granular and discrete along the entire line of the stab. There was never any growth spreading over the surface. Rosenow⁷ and Nickel² stated that the streptococcus cultivated from gastric ulcer would sometimes occur in irregular clumps and in tetrads and quatrads. The fused cocci resembling rods were frequently clumped together in the original growth but tetrads and quatrads were noted only in the peculiar staphylococcus contamination in the cultures.

Morphologically, the alpha and alpha-prime strains from foci in the mouth and human bites were practically the same as the gastric strain except that cocci were usually more round and rarely were definitely lanceolate. The first growth on a blood plate of one of the strains from an ulcer of the lip, cultures 37 and 38, which was one of the acute cases shown in table 2, was identical with a pneumococcus colony. However, on staining, long chains of gram-positive lanceolate streptococci were present. Rosenow⁷ claimed the transmutations of streptococci and pneumococci in 1916. It has been repeatedly observed that strains gain or lose hemolysis on artificial cultivation. This department is certain that the strains are recorded correctly and felt that it was desirable to call an unusual strain, faint hemolysis of which persisted, an alpha-alpha-prime. The hemolysis was not sufficient to term it an alpha-prime. This does not fall in with the accepted terminology (Brown) but is readily understood. This streptococcal type which is here reported as having been isolated from nearly 100 per cent of gastric, duodenal or gastrojejunal ulcers should therefore be termed a nonhemolytic streptococcus of the alpha type.

Fermentation and Other Cultural Tests.—The basal medium employed was semisolid (0.5 per cent) meat extract, 1 per cent peptone

agar, p_H 7, tinted with bromcresol purple as indicator. The sugars were added in 1 per cent strength for lactose, sucrose, salicin and inulin and 0.5 per cent for raffinose and esculin. Proper precautions were taken in sterilization. The fermentation reactions were recorded after four days' incubation at 37 C.

The single colony strains chosen for serologic work were put through seven sugars to determine fermentative reactions, with the following results: Eight of the ten type strains from ulcers of the stomach fermented lactose, sucrose and salicin, but did not ferment mannitol, raffinose, inulin or esculin. The other two strains fermented no one of these sugars by the method used. The five throat strains of table 2 also fermented lactose, sucrose and salicin and no other sugars, with the exception of one which fermented raffinose. Seven cultures obtained from ulcers on the hand, lip and mouth fermented lactose, sucrose and salicin but did not ferment mannitol, raffinose, inulin or esculin. Of the eleven strains isolated from the teeth or mouths of patients suffering from gastric ulcers, four different reactions were obtained with these test sugars. Two fermented lactose, sucrose and raffinose. Four fermented lactose, sucrose and salicin. Four fermented lactose and sucrose, and one fermented sucrose and mannitol. The gangrene strain fermented lactose, sucrose, salicin, mannitol and esculin; the erysipelas strain, salicin and mannitol. The strain obtained from the empyema of the thoracic cavity fermented sucrose and salicin. These three were beta strains. In the failure of the ulcer streptococcal strains to split mannitol and esculin, the relationship to mouth and throat types rather than to intestinal types is indicated.

These results, as will be seen later, indicate that the serologically identical organisms have the same fermentative reactions in practically 100 per cent and that those unrelated, serologically, are markedly heterogeneous.

An attempt was made to see whether the gastric streptococcus would grow in 0.5 per cent hormone agar acidified to the acidity of the stomach. Five tubes were made up with a hydrochloric acid content ranging from 0.5 to 0.1 per cent, respectively. Control tubes were also prepared with from 0.5 to 0.1 per cent sodium hydroxide content, respectively. The eleventh tube had a reaction of p_H 7.4. Growth occurred in the 0.1 and 0.2 per cent acid tubes and in the 0.1 and 0.2 per cent alkaline tubes. There was no growth in the 0.3, 0.4 and 0.5 per cent tubes of both acid and alkali. The growth in the control tube, p_H 7.4, was profuse. Therefore, the gastric streptococcus probably has not a special ability to grow in strongly acid medium. The gastric streptococcus does not grow in bile; gelatin is not liquefied after ten days, but milk is almost completely clotted. This is interesting because of the directly opposite results of others.

COMMENT

Morphologically and culturally, the nonhemolytic streptococcus isolated by certain other investigators (Rosenow, Nickel, Celler and Thalheimer) would seem to be identical with that recovered in this investigation. However, no agglutinogenic or antigenic studies have previously been made, and there is no certainty of specific relationship. When one reviews carefully the work of Krumwiede⁴⁸ in 1916 and that of Hooker⁴⁹ and his co-workers in 1929, the marked heterogeneity of the alpha type is convincingly proved. Hooker concluded that in the alpha type cross-agglutination and fixation tests have demonstrated a bewildering antigenic heterogeneity. He observed strong cross-agglutination in less than 3 per cent of 616 tests. No identical strains from different sources were discovered when a total of 2,057 colony strains were studied from 101 specimens. Group reactions occurred among fermentative heterologs as well as among strains of the same fermentative type. Antigenic unlikeness also features the identical colony strains derived from one individual.

It is therefore impossible to believe that alpha strains from such a wide variety of sources, such as teeth and tonsils and prostatic and cervical foci, could possibly be agglutinogenic and antigenic homologs or show a specific relationship with the gastric strain. One needs only to read Krumwiede or Hooker's review of the literature for evidence as to the homogeneity or heterogeneity of an individual's strains of streptococci to be convinced that all careful observations have consistently proved the extreme heterogeneity of the alpha type.

AGGLUTINATION INVESTIGATION

The following results show that the nine alpha strains from ulcers of the stomach are agglutinogenic and antigenic homologs and that they are identical with four other strains isolated from an acute specific disease. The tables also show the agglutinogenic and antigenic unlikeness to all the other strains, although some of these produce similar pathologic lesions, others, foci of infection, and all are culturally and morphologically similar.

Technic of Streptococcic Agglutination; Preparation of Immune Serums.—The growth from a twenty-four hour slant of hormone agar suspended in 1 cc. of saline solution is injected intravenously into rabbits without killing the organisms by heat or a chemical. On the first day, 0.2 cc., the second day, 0.4 cc., the third day, 0.4 cc., and on the fourth day, 0.6 cc., were injected. If the rabbit loses more

48. Krumwiede, C.: A Study of the Agglutination and Cultural Relationship of the So-Called Streptococcus-Viridans Group, J. Infect. Dis. **19**:760, 1916.

49. Hooker, S. F., and Anderson, L. M.: Heterogeneity of Streptococci Isolated from Sputum, with a Critique on Serological Classifications of Streptococci, J. Immunol. **16**:291, 1929.

than 50 Gm., the dose of the previous day is repeated. If the animal loses more than 100 Gm., no dose is given. After three days' rest, the rabbit is again inoculated for four days as follows: first day, 0.8 cc., second day, 1 cc., third day, 1.2 cc. and fourth day 1.4 cc. After a week a trial bleeding is made, and if the serum is of the proper titer the rabbit is bled to death. Otherwise, the second week's dosage is repeated.

Preparation of Antigen.—The strain of streptococcus is cultivated by daily replants in beef heart infusion peptone broth plus 2 per cent of sodium diphosphate and 0.1 per cent dextrose until a homogeneous growth suspension is obtained. If this suspension stays up overnight at 55 C. in this phosphate broth minus dextrose, the antigen is ready for use and can be made up in larger quantity. This is done by planting this homogenized culture in 200 cc. of dextrose broth, growing over night, washing three times in the aforementioned medium without dextrose and resuspending in phosphate broth to the proper concentration, which is about 3 billion per cubic centimeter. Solution of formaldehyde, 0.2 per cent is added, but no heat is used.

Technic of Set-Up: One-tenth cubic centimeter of the following dilutions is put in each of eight tubes:

Tube 1	1-10	Tube 4	1- 80	Tube 7	1- 640
Tube 2	1-20	Tube 5	1-160	Tube 8	1-1280
Tube 3	1-40	Tube 6	1-320	Tube 9	Saline solution and antigen

Nine-tenths cubic centimeter of antigen is added to each of these tubes, making a dilution of 1:100 in the first tube, 1:200 in the second tube, etc.

The tubes are left in the water-bath at 55 C. over night and a reading taken, the following symbols being used:

- ++ indicates complete agglutination—fluid clear.
- +1, nearly complete agglutination—slightly cloudy and fluid clumps smaller.
- +, 50 per cent complete.
- ±, slightly less than 50 per cent.
- 1, trace of agglutination.

Technic of Absorption.—The absorbing dose is the smallest dose of culture which when added to a certain amount of antiserum under suitable conditions will absorb all of its agglutinins. Testing with doses of 1:4, 1:10, 1:20, 1:30 and 1:40 usually covers the range of absorption. To test the absorptive capacity of other cultures, twice the volume is used. Broth cultures are centrifugated in accurately calibrated centrifuge tubes until the organisms are tightly packed. The amount is noted and the supernatant fluid decanted. Ten per cent is subtracted from the original reading, as all the broth cannot be poured off. The volume of cells is then multiplied by the absorbing dose which gives the total fluid to be used. This number minus the volume of organisms and divided by the serum dilution of 1:10 will give the amount of serum to be added. For example, using 0.4 cc. of packed cells and an absorptive dose factor of 10.

$$0.4 - 0.04 = 0.36 \times 10 = 3.6 - 0.36 = 2.24 \div 10 = 0.224$$

The 0.224 cc. of serum is added and the salt solution added to 3.6 cc.

The cocci are thoroughly mixed with diluted serum and placed in the water bath at 45 C. for two hours, being shaken at fifteen minute intervals. Tubes are then left in the icebox over night to complete absorption and centrifugated to clarify diluted serum. This serum is then used for agglutination tests with the

same dilutions used in the original test. Untreated diluted serum is carried through the same way as a control against the determination. This absorptive technic is modified after that of Dr. Anna Williams.

TABLE 6.—*Agglutination Data.*

Antigens	Serum 2	Serum 46	Serum 47	Serum 9	Serum 29	Serum 40
Gastric 2.....	6,400	3,200	6,400	6,400	6,400	800
Gastric 20.....	3,200	6,400	4,800	4,800	4,800
Gastric 23.....	6,400	6,400	6,400	6,400	4,800
Gastric 45.....	3,200	3,200	3,200	6,400	4,800
Gastric 46.....	6,400	6,400	6,400	6,400	6,400
Gastric 47.....	4,800	3,200	6,400	6,400	6,400
Gastric 53.....	6,400	3,200	3,200	4,800	3,200
Gastric 55.....	3,200	3,200	4,800	4,800	3,200
Gastric 56.....	3,200	3,200	6,400	6,400	3,200
Dog, gastric 9.....	3,200	6,400	6,400	6,400	3,200
Throat 29.....	6,400	3,200	6,400	3,200	6,400
Throat 38.....	3,200	3,200	3,200	3,200	3,200
Throat 39.....	4,800	3,200	3,200	3,200	6,400
Throat 44A.....	3,200	3,200	3,200	3,200	3,200
Mouth 15.....	200	100	200	200	100	800
Mouth 17.....	0	0	0	0	0	600
Lip 31.....	0	0	0	0	0	800
Lip 40.....	0	0	0	0	0	3,200
Lip 7.....	0	0	0	0	0	1,200
Hand 11.....	0	0	0	0	0	800
Hand 30.....	0	0	0	0	0	600

TABLE 7.—*Data of Agglutination and Absorption*

Agglutination with Serum 2									
Antigens	1:100	1:200	1:400	1:800	1:1,600	1:3,200	1:6,400	1:12,800	Control
Gastric 2	++	++	++	++	++	+1	+	$\frac{+}{1}$	—
Gastric 20	++	++	++	++	++	+	$\frac{+}{1}$	$\frac{+}{1}$	—
Gastric 23	++	++	++	++	++	+1	+	$\frac{+}{1}$	—
Gastric 45	++	++	++	++	++	+	$\frac{+}{1}$	$\frac{+}{1}$	—
Gastric 47	++	++	++	++	++	+1	$\frac{+}{1}$	$\frac{+}{1}$	—
Gastric 53	++	++	++	++	++	+1	+	$\frac{+}{1}$	—
Gastric 55	++	++	++	++	++	+	$\frac{+}{1}$	$\frac{+}{1}$	—
Gastric 56	++	++	++	++	++	+	$\frac{+}{1}$	$\frac{+}{1}$	—
Gastric 9	++	++	++	++	++	+	$\frac{+}{1}$	—	—
Throat 29	++	++	++	++	++	+1	+	$\frac{+}{1}$	—
Throat 38	++	++	++	++	++	$\frac{+}{1}$	$\frac{+}{1}$	$\frac{+}{1}$	—
Throat 39	++	++	++	++	++	+1	$\frac{+}{1}$	$\frac{+}{1}$	—
Throat 44A	++	++	++	++	++	+	$\frac{+}{1}$	$\frac{+}{1}$	—

Absorption of Serum 2							
Antigens	1:100	1:200	1:400	1:800	1:1,600	1:3,200	Control
Gastric 2.....	—	—	—	—	—	—	—
Gastric 20.....	—	—	—	—	—	—	—
Gastric 23.....	—	—	—	—	—	—	—
Gastric 45.....	—	—	—	—	—	—	—
Gastric 46.....	—	—	—	—	—	—	—
Gastric 47.....	—	—	—	—	—	—	—
Gastric 53.....	—	—	—	—	—	—	—
Gastric 55.....	—	—	—	—	—	—	—
Gastric 56.....	—	—	—	—	—	—	—
Gastric 9.....	—	—	—	—	—	—	—
Throat 29.....	—	—	—	—	—	—	—
Throat 38.....	++	+	1	—	—	—	—
Throat 39.....	—	—	—	—	—	—	—
Throat 44A.....	++	++	+	$\frac{+}{1}$	—	—	—

The agglutination and absorption tables are self-explanatory. Agglutination has been recorded in table 6 up to the point of 50 per cent agglutination. It will be noticed in table 7 that less than 50 per cent agglutination and a trace extends out to the highest titer 12,800 in practically all identical organism strains. There was slight agglutina-

tion in the absorption test of one of the throats, no. 39, recorded in table 8. This culture was obtained one week after the onset of the infection, and it had subsided markedly. This may account for the slight dissimilarity. The culture from throat 44A gave more marked agglutination and is probably not identical. The report should therefore state that only four alpha strains from the throat are absolutely identical serologically with the gastric strains. It should be noted that, as shown by table 9, when serum 40, an alpha-prime strain from an ulcer of the lip, was set up against the antigens of the other alpha-

TABLE 8.—*Data of Absorptions*

Antigens	Serum 2	Serum 46	Serum 47
Gastric 2.....	0*	0	0
Gastric 20.....	0	0	0
Gastric 23.....	0	0	0
Gastric 45.....	0	0	0
Gastric 46.....	0	0	0
Gastric 47.....	0	0	0
Gastric 53.....	0	0	0
Gastric 55.....	0	0	0
Gastric 56.....	0	0	0
Gastric 9.....	0	0	0
Throat 29.....	0	0	0
Throat 33.....	0	0	0
Throat 32.....	0	0	0
Throat 39.....	200	200	100
Throat 44A.....	400	300	400

* The zeros indicate no agglutination, which proves identical organisms when the agglutinins have been absorbed.

TABLE 9.—*Data of Strain from Ulcer of Lip Caused by Penetration of Tooth.*

Antigens	Serum 40								Control
	1:100	1:200	1:400	1:800	1:1,600	1:3,200	1:6,400	1:12,800	
Lip ulcer 40	++	++	++	++	+1	+	±	1	—
Teeth 15	++	++	+1	+	1	—	—	—	—
Teeth 17	++	++	+1	±	—	—	—	—	—
Lip ulcer 31	++	++	++	+	1	—	—	—	—
Hand ulcer 7	++	++	++	+1	±	1	—	—	—
Hand ulcer 11	++	++	++	+	±	1	—	—	—
Hand ulcer 30	++	++	++	±	1	—	—	—	—
Gastric 2	++	++	+1	+	±	—	—	—	—

prime strains and also against the antigen of gastric strain 2, there was 50 per cent agglutination to approximately 1:800. Previously, when the gastric strain serum had been set up against the alpha-prime antigen there was no agglutination. This would tend to strengthen the proof that only the gastric strain is a specific one, but that the alpha-prime strain is related and can stimulate some agglutinins for it. Absorption tests were not done with the alpha-prime strains, but they would probably not be identical because of their much lower degree of agglutination, approximately the same as the teeth alpha strains, which certainly are not identical.

PATHOLOGY OF ULCER

It seems most interesting and unique that Cruveilhier,¹⁷ one hundred years ago and thirty years before Pasteur and the discovery of the relation of micro-organisms to disease, should have described gastric ulcer as an inflammatory lesion typical of inflammation elsewhere; that Böttcher²³ in 1874, Gaillard²⁵ in 1882 and Letulle²⁴ in 1888 reported the presence of micro-organisms in stained tissue sections of gastric ulcer, that Sidney Martin¹⁵ in 1895 felt that gastric ulcer was identical "avec la nécrose bacterienne." Since that time, the inflammatory character of ulcer and the presence of micro-organisms in stained sections of gastric ulcer have been reported many times. Most authors report the organism as a diplococcus. Since ulcers resected at operation have been available for tissue sections, much more accurate descriptions have been made. Askanazy,⁵⁰ in 1924, reported that there were four typical zones noted in the ulcer: (1) exudation, (2) fibrinoid necrosis, (3) granulation, and (4) cicatrization. According to Karsner,⁵¹ the exudation may be purulent, sanguinopurulent, fibrinopurulent or catarrhal. Granulation tissue is variable in extent and is not different from granulation tissue elsewhere. It appears early in the course of the ulcer and is still present in large old ulcers. In many of the early ulcers, there is a fairly widespread acute gastritis which may be superimposed on the chronic hypertrophic gastritis, which in the experience of these authors accompanied a large number of ulcers of all stages. This fact has been noted repeatedly, and it is of interest to hear surgeons state that when a stomach is resected the gastric mucosa seen does or does not look like the mucosa seen when an ulcer is present. It is the typical l'état mamelonée, first described by Virchow in alcoholic gastritis, which is almost constantly found when ulcer is present. Karsner⁵¹ concluded by saying that, pathologically, peptic ulcer is an inflammatory lesion so situated that gastric juice probably emphasizes the destruction of tissues, and that the inflammation is primary is suggested but is not proved. He deviated from his pathologic description to say that hyperacidity, stasis, whether of neuromuscular or obstructive origin, the irritative and traumatic influence of gastric contents and the traction of muscle about the ulcer are primary factors.

In 1923, after studying many sections of gastric ulcer, Stewart⁵² stated that he believed that the most common cause of acute ulcer was bacterial infection.

50. Askanazy: Ueber Bau und Entstehung des chronischen Magengeschwürs sowie Soorpilz befunde in ihm, Virchows Arch. f. path. Anat. **234**:111, 1924; **250**:370, 1924.

51. Karsner, Howard T.: The Pathology of Peptic Ulcer, J. A. M. A. **85**: 1376 (Oct. 31) 1925.

52. Stewart: The Pathology of Gastric Ulcer, Brit. M. J. **2**:955, 1923.

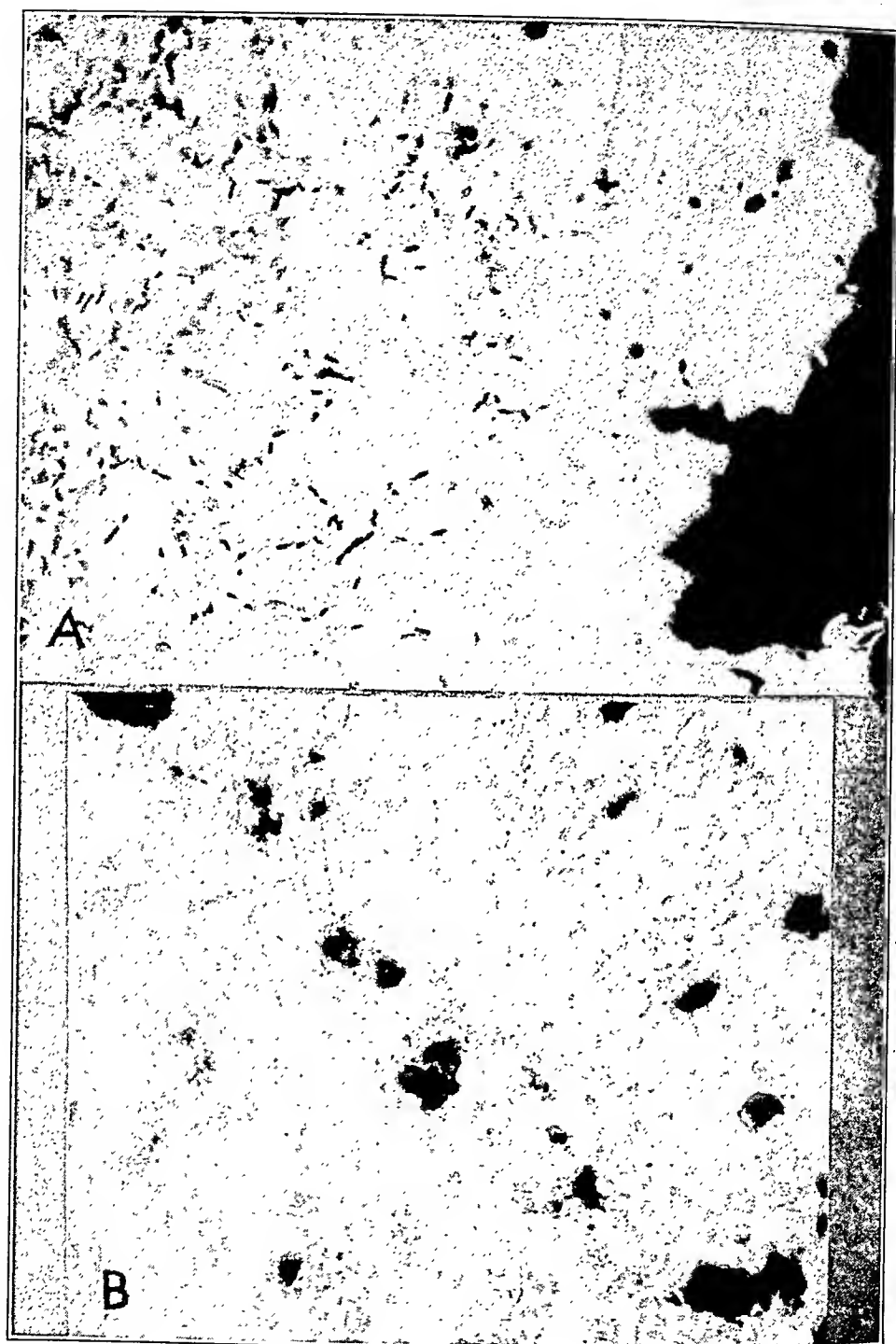


Fig. 2.—*A*, Levaditi tissue section of ulcer showing the destroyed surface covered with coccus and bacilloid forms which comprises the necrotic rim of the crater spoken of previously. *B*, Levaditi tissue section of ulcer showing sanguino-exudate with many degenerating phagocytic white cells.

McCarty⁵³ concluded from the pathologic study of material from 216 partial gastrectomies that, after the initial destruction of the mucosa, ulcers deepened by necrosis, and that the deepening was sufficiently slow to allow a definite dense connective tissue barrier against perforation to be formed.



Fig. 3.—Levaditi tissue section of ulcer showing the irregular destroyed glandular surface with many diplococci and bacilloid forms.

This department wishes to report its conclusions following the study of serial Levaditi sections of many gastric ulcers. Four are those in which the streptococcus was recovered in culture. Small pieces were cut immediately on resection in the operating room and fixed in 10 per cent neutral solution of formaldehyde. They were then carried

53. McCarty, N. C.: Pathological and Clinical Significance of Stomach Ulcer from the Study of Material from 216 Partial Gastrectomies, *Surg. Gynec. Obst.* **10**:449, 1910.

through and stained by the method of Levaditi. When fixed immediately in this manner, a rim of streptobacilli was always present covering the necrotic surface of the mucous membrane as shown in figure 2 *A*. Single cocci, diplococci, streptobacilli and bacilli were constantly present in the purulent, sanguinopurulent, fibrinopurulent or catarrhal exudate which forms the surface of the ulcer, as shown in figure 3 and figure 2 *A*. Phagocytic white cells showing large stained granules were numerous in the sanguino-exudate (fig. 2 *B*).

The organisms were practically never found below the submucosal layer, and never in the muscular layers. If the base of the ulcer was a cicatrized muscle layer, the mucosa having been entirely destroyed, no organisms could be found. The glands of the mucosa adjacent to the exudative necrotic crater would invariably show organisms and beginning destruction. The mucosa not adjacent to the crater appeared normal, and the rim of organisms on the surface stopped.

It would appear, therefore, that the inciting organism attacks the mucosa directly, causing its destruction or necrosis, leaving a cicatrized or granulating base and never invading the muscular layers. It would be difficult to say or to prove by the morphologic appearance of the organisms in the Levaditi sections whether or not they are the streptococci recovered in culture. Some are definitely bacilli and morphologically appear as colon bacilli. The greatest number, however, resemble the first growth of the streptococci in hormone agar, that is, single and diplococci and fused cocci appearing as small bacilli or rods. Mouth spirochetes and fusiform bacilli were questionably present once or twice. It is this department's belief that the primary organism is the streptococcus, for it is always found in the most numbers and only infrequently associated with others. Its varying morphologic appearance can easily be accounted for when one sees its appearance on primary culture, changing markedly under artificial cultivation.

In 1928, Leriche⁵⁴ stated that gastric ulcer was a disease of the emptying stomach, not of the digestive stomach. He believed, therefore, that the type of gland in which the ulcer occurred should be investigated. Cogniaux,⁵⁵ therefore, examined 45 specimens and found that the ulcer occurred in the region of the pyloric glands 25 times, in the glands of Brunner 6 times, 9 times partly in pyloric and partly in duodenal, 3 times in pyloric and fundic and only 2 times in fundic glands alone. He believed, therefore, that in 95 out of 100 cases the ulcer occurs in the mucous secreting alkaline glands. His pathologic

54. Leriche, M. R.: Examen critique des idees sur le traitement des ulceres gastro-duodenaux, *Bull. et mém. Soc. nat. de Chir.* **55**:233, 1929.

55. Cogniaux: Sur le developpement presque exclusif des ulceres gastriques en milieu de glandes a mucus, *Presse méd.* **36**:589, 1929.

description is similar to those previously stated. He found that which has been stated many times before—that hypertrophic, atrophic and metaplastic gastritis accompanies ulcer.

Experimental Pathologic Conditions.—An attempt was made to reproduce an ulcer in the stomach of a dog by the direct injection into it of the alpha streptococcus recovered from a human gastric ulcer. In two dogs at laparotomy, 0.5 cc. of a twenty-four hour broth culture was injected directly into the muscular or submucosal layers of the lesser curvature just proximal to the pylorus with a syringe and small caliber needle. Sterile incubated broth was injected just proximal to this. Cultures 2 and 3 were used. Twenty-five days later the dogs



Fig. 4.—*A*, ulcer of upper lip following penetration of a tooth. Culture strain 7 and 8. *B*, ulcer of lower lip following penetration of tooth. Culture strain 40. *C*, complete loss of lower lip following blow in the mouth and complicated erysipelas. Culture strain 31. *D*, ulceration of knuckle joint following repeated contact of small abrasion with mouth. Culture strain 30. *E*, superficial ulceration extension only involving dermis following penetration of tooth. Culture strain 26. *F*, ulcer of knuckle following penetration of tooth. Culture strain 5-6.

were reoperated on, and that area of the stomach excised, examined and cultures made. The muscular layers were greatly thickened; the overlying mucosa was slightly blue; the site of injection of sterile broth could not be differentiated from the normal stomach wall, and there was no ulceration of the mucosa underlying the site of injection. The organism was recovered from the site of injection of culture 2.

At operation, before an attempt was made to excise this area, the most rigid reverse peristalsis coming up the duodenum and extending

on the stomach only to the site of injection occurred. It was a most remarkable rigid contraction and occurred about every half minute, lasting from fifteen to twenty seconds. It seemed quite logical to assume that if this were a common occurrence it could well explain pain and the inability of an ulcer to heal.

It was felt that the organism would have to be injected directly into the mucosa, for when injecting through serosa one could not be sure of the exact layer into which the injection was going. Injection of a twenty-four hour broth culture was therefore made into the mucosa about the pylorus at laparotomy by opening the stomach on the greater curvature and forcing the mucosa of the lesser curvature through it. Many small blebs with the culture were made proximal to the pylorus. It is impossible to raise a superficial bleb in duodenal mucosa as it is extremely friable and rubs off easily. This may have some bearing on the site of ulcer being extremely common in the duodenum, which is easily injured.

A black silk thread which had been left in a twenty-four hour broth culture was passed under the submucosa by means of a longitudinal incision through the muscle layers of the lesser curvature just proximal to the pylorus, and then left in place, the muscle layers being closed over it.

After two months, both of these dogs were reoperated on. The mucosa of the first was normal, not showing any pathologic change. There was only scar tissue present in the second dog, and the alpha streptococcus was not obtained by cultures made from the thread which was lying in the muscle layers with normal underlying mucosa and adjacent stomach wall. Both of these dogs had received injections of culture 23d. As it was believed that artificial cultivation might reduce the virulence of the organism, the first growth obtained of cultures 47b and 53 was injected into the mucosa of the respective dogs described previously. Forty-five days later, at reoperation, the mucosa in both dogs appeared normal in every respect.

It would therefore seem that the intramuscular or submucosal injection of the alpha streptococcus cultivated from human ulcers will not produce an ulcer in the dog in this manner. It is interesting, however, that with intramuscular injection there was considerable thickening and induration after twenty-five days and that the organism was recovered.

All the rabbits that were used in the preparation of the serum and that received repeated small intravenous doses of the living organisms washed in sterile saline solution, at autopsy showed no lesions of the stomach or duodenum. Six rabbits died after losing weight rapidly before their serum had reached a high enough titer to use, but showed no pathologic change except small pneumonitis patches.

This would strongly bring out the possibility that those experimenters who have produced hemorrhagic erosions and small ulcerations of the duodenum by large intravenous doses of various broth cultures of streptococci were doing so by a foreign protein anaphylactic type of reaction, which one may easily produce with peptone.

The ulcers produced by the intracutaneous injection in the dog's skin of the alpha streptococcus obtained from human ulcers as shown in *B* and *C* of figure 5, are proof enough of its pathogenic powers. Although smaller than those produced by the alpha-prime strain, the chronicity was the same. They were clear, punched-out ulcers which involved only dermis.

The largest ulcer, the middle one (fig. 5 *A*), was produced by an alpha-prime strain recovered by Dr. John Torrey from ulcerative colitis.

The first injections were made subcutaneously, and by this method a lesion was never produced. Only by intradermal injection did an ulcer result. This demonstrates its specificity for dermis; the specificity for mucous membrane is indicated by the fact that the lesions of the mucous membrane of the mouth were always superficial.

These laboratory animals are not subject to spontaneous gastric ulcers and probably enjoy a normal resistance to the causative organism. One could hardly expect to produce these ulcers by a single injection of such a low grade virulent organism as the alpha streptococcus.

AGGLUTINATION OF PATIENTS' SERUMS WITH PROVED GASTRIC ULCER AGAINST THE ANTIGEN OF THE ALPHA GASTRIC STRAIN

Because of the failure of the intradermal skin sensitivity test to cause any more reaction in a patient suffering from gastric ulcer than in one without gastric ulcer, it was felt that the organism did not create a toxin that might circulate in the blood in sufficient amount to produce general sensitization but only a localized toxin. The material used for the test was a filtrate of broth cultures of the gastric alpha streptococcus prepared by the same method as that used for the scarlet fever toxin and supplied to this department by the Lederle Antitoxin Laboratories. It was therefore decided to see whether serum obtained from patients suffering from proved gastric ulcer would contain specific agglutinins for the alpha streptococcus obtained from gastric ulcer.

The following series of thirty-eight patients with proved gastric ulcer, controlled with serum from thirty patients suffering from other types of streptococcus infection, show the encouraging results obtained.

It is apparent from tables 10 and 11 that the most marked agglutination occurs in the most active ulcers, namely, bleeding and perforated. Less marked agglutination occurs in patients who have been under rigid medical treatment for a varying length of time and also in those

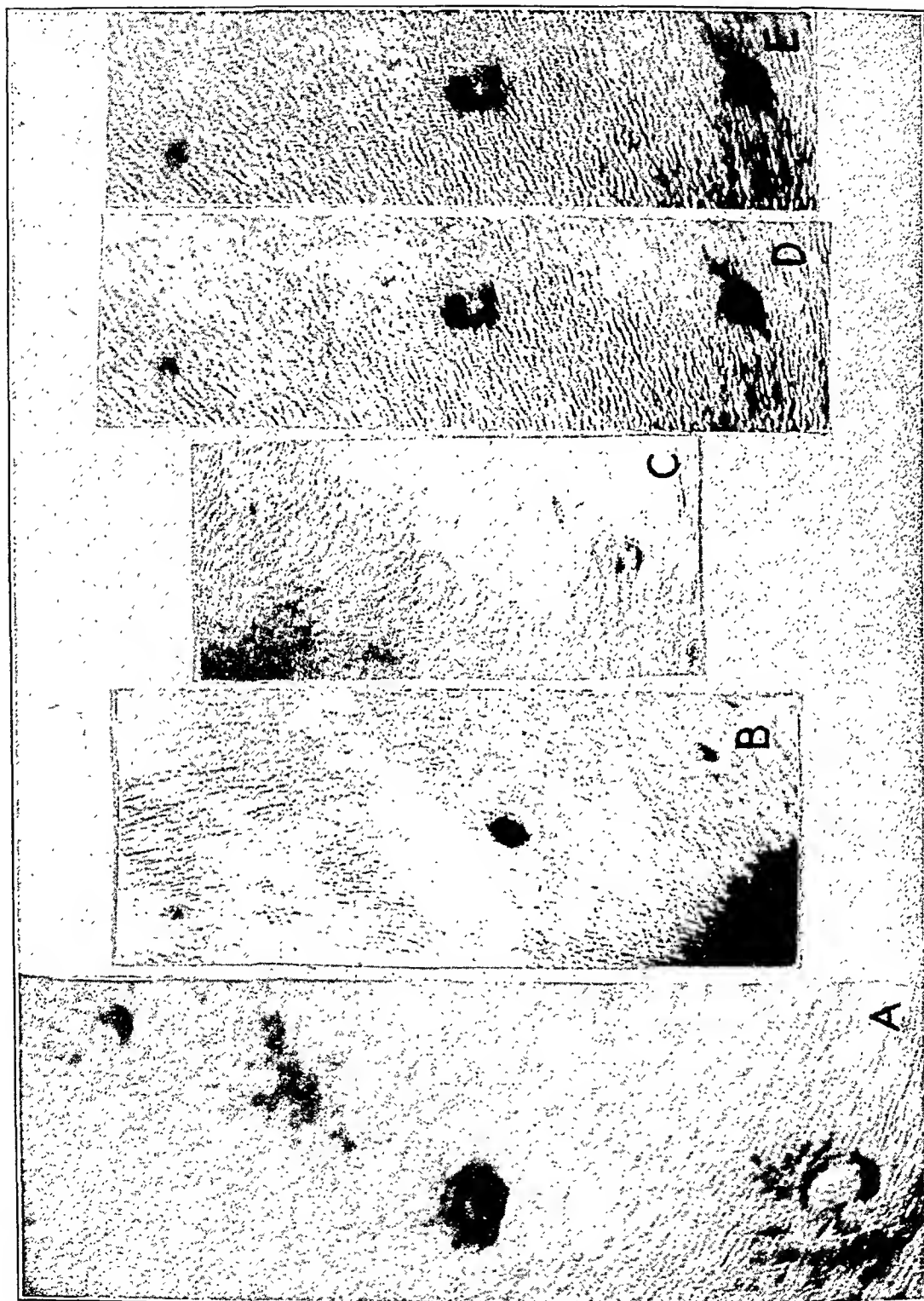


Fig. 5.—The ulcers produced in the skin of the dog shown in the photographs were produced by making injections of 0.5 cc. of a twenty-four hour dextrose broth culture intradermally. *A*, top, alpha-prime strain, culture 5-6; center, ulcerative colitis alpha-prime strain, Dr. Torrey; bottom, alpha-prime strain, culture 11. *B*, top, gastric strain, culture 11; center, alpha-prime strain, culture 31; bottom, gastric strain, culture 19. *C*, top, gastric strain, culture 23; center, alpha-prime strain, culture 26; bottom, alpha-prime strain, culture 30. *D*, top, gastric strain, culture 47; center, alpha-prime strain, culture 40; bottom, gastric strain, culture 53. *E*, same as *D*, one week later.

in whom pain has recurred without other symptoms for a varying number of years after the ulcer symptoms had been completely relieved. In this type of case, operation usually reveals not an active ulcer but periduodenal adhesions from previous inflammation. It was only in this type that the 1:40 agglutination titer in the ulcer series occurred. None of the serums of the control series went above the 1:40 titer, most of them showing not more than 50 per cent agglutination at 1:20.

A most interesting case is that of R. R. in table 10. This patient had had a gastro-enterostomy six years previously for a duodenal ulcer and had had recurrent symptoms since then. His serum agglutinated to 1:1,280 before operation. A resection was done, and a large gastro-jejunal ulcer was found perforating into the colon together with a scarred, practically healed duodenal ulcer. The organism 55 was isolated from the gastrojejunal ulcer, and the scarred healed duodenal ulcer was found sterile. Thirty-six days after resection, his serum agglutinated only to 1:80.

In tables 10 and 11, the highest serum dilution agglutinating the antigen 50 per cent is recorded as the titer. The tests were carried out macroscopically.

COMMENT

The outstanding facts which favor an infectious theory of gastric ulcer are:

1. An alpha streptococcus can be cultivated from practically 100 per cent of active ulcers, in pure culture in a majority of cases.
2. By agglutination and agglutinin absorption, the alpha streptococcus has been proved to be an identical organism. This homogeneity in itself is remarkable because of the proved heterogeneity of the alpha group.
3. The organism has a tendency to form ulcers and attack skin and mucous membrane. It is related but not identical with the alpha-prime strains that are found in ulcers of the skin.
4. The serum of patients suffering from peptic ulcer contains this organism's specific agglutinins, seemingly to a degree proportional with the size, stage and extent of the ulcer. Control serum from non-streptococcal pathologic conditions and serum from patients suffering from other types of streptococcus infection contain much less agglutinins for this organism, generally less than 25 per cent of the amount.
5. Pathologically, the lesion is typical of inflammation elsewhere. The necrotic membrane in the crater of the ulcer is a common manifestation and contains these organisms. Examination of the fresh specimen reveals this condition.

TABLE 10.—Agglutination of Serum of Patients with Proved Gastric Ulcer with Antigens of Two or Three Gastric Strains*

Patient	Service†	Ulcer	Symptoms	Duration	Treatment	Gastric Antigen					
						2	23	47b	Strain		
P. B.	M4	Perforated duodenal	2 years	2 years	None	1280	1280	1280	1280	55	
R. R.	M4	Bleeding gastro-jejunal ulcer	Gastro-enterostomy for 6 months	Gastro-enterostomy for duodenal ulcer 6 years previously; recurrent symptoms	None	1280	1280	1280	1280		
J. Y.	L4	Perforated duodenal	10 years	Blood obtained 5 days after simple suture for perforation	None	1280	1280	1280	1280		
L. M.	M4	Gastric	Gastro-enterostomy 6 months previously; symptoms, 5 years	Gastro-enterostomy 4 years previously; recurrent symptoms for 3 years	Diet powders	160	320	320	320	56	
E. D.	A1	Duodenal gastro-jejunal	Gastro-enterostomy 6 months previously; symptoms, 5 years	Gastro-enterostomy 4 years previously; recurrent symptoms for 3 years	Diet powders	160	320	320	320		
P. P.	M4	Perforated duodenal	Simple suture for perforation; symptoms only 5 weeks previously	Simple suture for perforation; symptoms only 5 weeks previously	Simple suture	320	320	320	320		
G. N.	M6	Perforated pyloric	Simple suture; no induration; no previous symptoms	Simple suture; no induration; no previous symptoms	Simple suture	80	80	80	80		
J. A.	L6	Perforated duodenal	2 months	Sudden perforation; simple suture	Simple suture	320	320	320	320		
W. F.	M4	Perforated gastric	3 years	Simple suture; blood 5 days after operation	Simple suture	160	160	160	160		
D. M.	L6	Duodenal	Perforated and simple suture, 1926; gastro-enterostomy for recurrent symptoms; ulcers present	Perforated and simple suture, 1926; gastro-enterostomy for recurrent symptoms; ulcers present	Perforated and simple suture, 1926; gastro-enterostomy for recurrent symptoms; ulcers present	320	320	320	320		
H. H.	M3	Pyloric	6 months	Gastro-enterostomy for pyloric ulcer 9 days before	Gastro-enterostomy for pyloric ulcer 9 days before	160	160	160	160		
A. W.	M5	Perforated pyloric	Blood taken thirtieth day after gastro-enterostomy	Blood taken thirtieth day after gastro-enterostomy	Blood taken thirtieth day after gastro-enterostomy	80	80	80	80		
H. J.	M5	Bleeding gastric	Severe for 2 years	Severe for 2 years	Severe for 2 years	320	320	320	320		
H. C.	M6	Duodenal (x-ray)	Severe in spring	Severe in spring	Severe in spring	160	160	160	160		
C. O.	C. O.	Duodenal (x-ray)	3 years	Recurrent 1 year, pain	Recurrent 1 year, pain	40	40	40	40		
J. K.	L6	Duodenal (x-ray)	6 months	Severe 1 week	Severe 1 week	160	160	160	160		
W. K.	C. O.	Duodenal (x-ray)	6 months	Not severe	Not severe	40	40	40	40		
A. 4567	1st Surgical	Postpyloric (x-ray)	6 months	6 months	6 months	160	160	160	160		
M. W.	1st Surgical	Duodenal (x-ray)	Mild	1 year	1 year	160	160	160	160		
I. O.	1st Surgical	Duodenal (x-ray)	Mild	6 months	6 months	160	160	160	160		
J. C.	1st Surgical	Duodenal (x-ray)	Mild	6 months	6 months	160	160	160	160		
C. M.	2d Surgical	Duodenal (x-ray)	Pain for 6 months	Known ulcer for 6 years	Known ulcer for 6 years	320	320	320	320		
J. F.	2d Surgical	Duodenal (x-ray)	Pain for 6 months	Known ulcer for 6 years	Known ulcer for 6 years	320	320	320	320		
A. 45671	C. O.	Postpyloric (x-ray)	Mild	2 years	2 years	80	80	80	80		
J. B.	L5	Gastric, perforated	Mild before perforation	2 years	2 years	160	160	160	160		
Dr. M.	Private	Duodenal	Healed recurrent	2 years	2 years	320	320	320	320		
H. G.	C. O.	Duodenal (x-ray)	Recurrent pain	2½ years	2½ years	160	160	160	160		
A. 45813	C. O.	Postpyloric (x-ray)	Pain	2 months	2 months	80	80	80	80		
A. 45471	C. O.	Postpyloric (x-ray)	Mild	1½ years	1½ years	80	80	80	80		
J. B.	M6	Large old gastric	Severe	10 years	10 years	80	80	80	80		
J. N.	M4	Duodenal (x-ray)	Only pain	2 years	2 years	160	160	160	160		
A. G.	M4	Pyloric (x-ray)	Obstruction	10 years	10 years	80	80	80	80		
A. 45483	C. O.	Duodenal (x-ray)	Pain	8 years	8 years	160	160	160	160		
A. 46085	C. O.	Pyloric (x-ray)	Pain	3 months	3 months	160	160	160	160		
L. O.	C. O.	Duodenal (x-ray)	Pain	2 to 3 years	2 to 3 years	80	80	80	80		
J. J.	L4	Gastric	Pain, indigestion	6 years; recurrent for 3 weeks	6 years; recurrent for 3 weeks	160	160	160	160		
H. J.	L4	Duodenal	Pain	2 years	2 years	320	320	320	320	58	
J. C.	1st Surgical	Duodenal (x-ray)	Pain	1 year	1 year	80	80	80	80		
T. T.	1st Surgical	Duodenal	Typical pain	5 weeks	5 weeks	160	160	160	160		
R. R.	M4	Duodenal	34 days after resection, gastrojejunal ulcer	Before resection, agglutination 1280	Before resection, agglutination 1280	80	80	80	80		

* Set-ups 11950 were used in the first three experiments and 1:320 in all the rest. Gastric strain 58 was recovered too late to homogenize and agglutinate in the present study. It was not included. It was deemed unnecessary to continue the three antigens throughout, as the results had been proved identical serologically. In this column, wards M1, L1 and M5 are in the Second Surgical and wards M6 and L6, the First Surgical. Clinics of Bellevue Hospital; C.O. indicates Cornell Clinic.

6. The rapidity with which an ulcer, no matter how large, will heal following simple suture and not recur for many years or not at all is certainly against any trophic disturbance. Leriche⁵⁴ has noted the remarkable results following simple suture when the ulcer was so large

TABLE 11.—Control Series of Patients with Normal Serum Showing Incidence of Foci of Infection

Patient	Service	Disease	Focus of Infection	Agglutination		
				2	23	47b
D. O.	M4	Chronic osteomyelitis.....	Bone.....	40	20	20
P. D.	L5	Chronic cholecystitis; duodenitis; cholecystectomy	Gallbladder.....	40	20	20
A. R.	M5	Chronic cholecystitis; duodenitis; cholecystectomy	Gallbladder.....	40	40	40
L. P.	M5	Giant cell sarcoma.....	Bone.....	20	20	20
M. E.	M5	Ovarian cyst and salpingitis	Fallopian tube.....	40	40	40
J. G.	M4	Hernia.....	None.....	20	20	20
L. M.	M4	Gastric hemorrhage; no ulcer by roentgen examination	Cirrhosis of liver.....	40	40	40
J. M.	M4	Repeated gastric hemorrhage; multiple transfusions; fatal hemorrhage	Autopsy; large carcinoma of lesser curvature; direct extension through liver	20	20	20
H. H.	M3	Ulcer symptoms; not operated on	X-ray repeatedly negative...	40	40	40
A. 45419	C.C.	Ulcer symptoms.....	X-ray repeatedly negative...	40	40	40
A. 45576	C.C.	Ulcer symptoms.....	X-ray repeatedly negative...	40	40	40
A. 45509	C.C.	Ulcer symptoms.....	X-ray repeatedly negative...	20	40	20
C. R.	M4	Cellulitis of arm.....	Soft parts; streptococcus and staphylococcus	40	40	
J. D.	M4	Hernia.....	Bad teeth.....	40	40	
J. G.	M4	Cellulitis of knee.....	Soft parts; streptococcus and staphylococcus	40	40	
W. M.	M4	Hernia.....	Bad teeth.....	40	20	
T. S.	M4	Carcinoma of rectum.....	Bad teeth.....	40	40	
S. H.	L4	Hemorrhoids.....	None.....	40	40	
M. S.	L4	Hernia.....	None.....	20	20	
S. S.	L4	Hernia.....	None.....	40	40	
H. P.	L4	Hemorrhoids.....	Bad teeth.....	40	40	
H. A.	L4	Compound fracture.....	None.....	40	40	
T. M.	L4	Hernia.....	Bad teeth.....	40	40	
D. S.	A1*	Acute rheumatic fever; acute endocarditis; acute pain in joints	Teeth, tonsils.....	40	40	
F. H.	A1	Acute multiple arthritis...	Teeth, tonsils.....	40	40	
T. L.	B1	Multiple infectious arthritis	Teeth, tonsils.....	40	40	
J. A.	A1	Acute infectious arthritis..	Teeth, tonsils.....	40	40	
M. F.	Ground B	Acute infectious multiple arthritis	Teeth, tonsils.....	40	40	
R. P.	Ground B	Acute infectious arthritis..	Teeth, tonsils.....	40	40	
M. S.	Ground B	Acute rheumatic fever multiple joints	Teeth, tonsils.....	40	40	
C. R.	Ground B	Multiple infectious arthritis	Teeth, tonsils.....	40	40	
V. A.	Ground B	Acute infectious multiple arthritis	Teeth, tonsils.....	40	40	

* A1, B1, Ground B, from Second Medical Clinic, Cornell.

and so fixed that it could not be resected. If the ulcer were due to a trophic disturbance, such rapid healing could not possibly take place. That acidity is a secondary factor is favored by the fact that the great majority of ulcers occur in the area in which there are alkaline mucous secreting glands. Also, the acidity of the stomach is normal or less than normal in more than 50 per cent of cases of gastric ulcer.

Smithies,⁵⁶ in his review of 2,168 cases of peptic ulcers, classified 33.1 per cent as due to infection; 2.6 per cent had no free hydrochloric acid. In 23 per cent, the free hydrochloric acid was below 30, in 41 per cent the free hydrochloric acid values were within the normal range (41 to 50 per cent) and in 33.4 per cent the values were greater than normal.

Acid values, however, probably depend on stasis, the result of spasm or cicatrization, preventing regurgitation of alkaline duodenal contents. Elman⁵⁷ has shown the much slower neutralization of an acid test meal in patients with ulcer than in normal patients. Following gastroenterostomy in patients with ulcer, he found that the acid test meal corresponded to that of the normal.

It is probably the spasm, muscle tension and fixation that irritate and prevent healing of the ulcer and not the occasional higher acidity, which is secondary.

Holland⁵⁸ found that postpyloric ulcer was five times as common as gastric ulcer and believed that the pars pylorica, the muscular activity of the antrum and valve itself plays an important part, if not in the actual beginning of the disease, at least as a factor which prevents healing.

Anatomically, the duodenum is the region of greatest fixation and the poorest and most tortuous blood supply, as demonstrated by Reeves.⁵⁹ The preponderance of ulcer in males may be due to the much greater fixation of the duodenum than in females, as brought out by Wilkie.⁶⁰ The good results following resection, therefore, could be due to the fact that it does away with fixation and spasm and leaves a freely movable stomach. Certainly all of the acid secreting glands are not removed by a subtotal resection, for the acid secreting glands extend to the esophagus.

A premise might therefore be made that peptic ulcer is caused by a streptococcus of the alpha type of low grade virulence, which has a tendency to produce ulcers attacking skin or mucous membrane; that it extends and progresses only in the mucous membrane and necrotic surface of the crater; that the underlying layers of the stomach are unable to withstand the continual action of the contents of the stomach as the mucous membrane can and healing is prevented by the resulting

56. Smithies, Frank: Significance of Etiological Factors in the Treatment of Peptic Ulcer, *J. A. M. A.* **74**:1555 (June 5) 1920.

57. Elman, R.: The Behavior of Gastric Acidity in Duodenal Ulcer and Pyloric Obstruction Before and After Gastroenterostomy, *Surg. Gynec. Obst.* **49**:34, 1929.

58. Holland: Post Pyloric Ulcer, *M. Clin. N. Amer.* **8**:232, 1924.

59. Reeves, quoted by Massie: A Synopsis of Views Held by American Authors as to Causation of Gastric Ulcer, *Guy's Hosp. Gaz.* **35**:374, 1921.

60. Wilkie, D. P. D.: Duodenal Ulcer, *Lancet* **2**:1228, 1927; Observation on the Pathology and Etiology of Duodenal Ulcer, *Edinburgh M. J.* **13**:196, 1914.

spasm of a fixed area; that the organism may remain quiescent in the mucous membrane for varying lengths of time depending on the general resistance of the patient, and recurs when other infections are prevalent.

Probably foci of infection play no part, except to aid in lowering the patient's vitality. In reviewing 556 cases, Emery and Monroe⁶¹ recently found that foci of infection were not any more common than with any other group. The great majority of patients at Bellevue Hospital have notoriously bad teeth, but this is not any more prevalent in patients with ulcer than in any other group.

Frick,⁶² Wilkie⁶⁰ and Coffey⁶³ concluded from their clinical experience that foci of infection, giving off infected streptococcal emboli with an affinity for gastric and duodenal mucosa, are the initiating cause of ulcer. Coffey goes so far as to state that if foci of infection could be eradicated no patient with ulcer would come to operation.

Jackson, in reviewing many esophageal ulcers, found that local treatment with the aid of the esophagoscope and the eradication of foci of infection usually resulted in the healing of the ulcer.

The evidence here presented showing nonrelationship of the alpha strains from foci in the teeth with the gastric alpha strain rules out this belief.

The spirochetes and fusiform bacilli are by far the most frequent organisms seen in sections of the gum tissue and granulomas at the base of infected teeth, as shown in figure 5 *A*. Streptococci are infrequent. The alpha streptococcus obtained from the base of teeth was not found to be related to the stomach strain serologically.

The most difficult question to answer is, How does this organism get a foothold in the mucosa of the stomach and duodenum? Does the gastritis usually found in practically every case precede or follow? There must be some preceding pathologic change or a localized lowered resistance; otherwise, everyone would be likely to suffer from gastric ulcer. Low grade organisms of this type could not possibly gain a foothold without lowered resistance.

Infants aged from 1 to 6 months, which is the age of incidence of more than 100 reported cases of death due to duodenal ulcer, probably do not have a previous pathologic condition; certainly they have no foci of infection in the teeth, and their only intake is milk. They are all marasmic infants whose resistance to any type of infection is greatly lowered, and the cases seem to occur epidemically. In this way they

61. Emery, E. S., and Monroe, R. T.: Peptic Ulcer: A Study of Five Hundred and Fifty-Six Cases, *Arch. Int. Med.* **43**:846 (June) 1929.

62. Frick, A.: Medical Treatment of Gastric Ulcer Without Alkalis, *J. A. M. A.* **82**:595 (Feb. 23) 1924.

63. Coffey, R. C.: Personal Experience in Peptic Ulcer, *J. A. M. A.* **91**:1 (July 7) 1928.

resemble the occasional outbreaks of severe streptococcic infections of the throat which have been proved to have their source in cow's milk. Jones⁶⁴ found hemolytic and faintly hemolytic streptococci commonly in both pasteurized and unpasteurized milk. Because of the organisms' power to resist heat which is practically that of pasteurization, it is possible that this organism might have the same source.

The success claimed by some⁶⁵ for foreign protein shock therapy, injections of milk, in the treatment of ulcer could be attributable only to its known effect on micro-organisms.

SUMMARY

The following facts have been established which demonstrate clearly the specificity of the alpha streptococcus obtained from gastric ulcer:

1. The proof obtained by experiment that a nonhemolytic streptococcus of the alpha type, isolated from nine resected gastric, duodenal and gastrojejunal ulcers, was an agglutinogenic and antigenic homolog.

2. Its agglutinogenic and antigenic unlikeness with all alpha strains from foci of infection such as the teeth.

3. Its agglutinogenic and antigenic identity with four alpha strains obtained from four cases of an acute specific disease, characterized by small ulcers of the lip, tongue, buccal membrane and tonsils.

4. Their relation to alpha prime strains producing ulcers of the skin.

5. Their specific agglutination with serums from patients with proved gastric, duodenal or gastrojejunal ulcers controlled against serums from patients with other types of streptococcus infection.

6. The organisms' apparent presence in the lesion in immediately prepared Levaditi tissue sections.

7. The ability to produce ulcer and its relation to an alpha-prime strain definitely producing ulcer. The possibility of their source being cow's milk has been suggested.

If in a large series of cases specific agglutination of the gastric alpha strain continues, which it gives every indication of doing, this department's efforts will be aimed primarily toward determining its source and prevention, and secondarily toward a real vaccine therapy.

16 East Ninetieth Street.

64. Jones, D. G.: Hemolytic Streptococci Found in Milk, *J. Infect. Dis.* **19**: 236, 1916.

65. Martin, L.: Peptic Ulcer; the Effect of Parenteral Injections of Purified Milk Proteins on the Symptoms and Progress, *Arch. Int. Med.* **43**:299 (March) 1929.

THE RELATION OF THE DISTRIBUTION AND STRUCTURE OF THE CORONARY ARTERIES TO MYOCARDIAL INFARCTION*

MERRITT B. WHITTEN, M.D.

Fellow in Medicine, Mayo Foundation

ROCHESTER, MINN.

A description of the usual course of the coronary arteries and of their more common variations is necessary for the present study. As a detailed account of the finer branches of the coronary arteries is of no particular value in understanding the present work, an elaborate description of the vessels will not be presented, and an account of the auricular circulation will be omitted entirely.

THE USUAL DISTRIBUTION AND THE MORE COMMON VARIATIONS OF THE BLOOD VESSELS SUPPLYING THE VENTRICLES

The Typical Course of the Coronary Arteries.—Both coronary arteries arise from the aorta close to its juncture with the ventricle. The right coronary artery originates from the anterior sinus of Valsalva, and passes to the coronary sulcus. It follows along this groove at the juncture of the right auricle and the right ventricle, and gives off branches to the anterior surface of the right ventricle. One or two of these branches extend anteriorly across the conus arteriosus for about half the distance toward the anterior interventricular sulcus, and they usually end in an anastomosis with similar branches from the anterior descending branch of the left coronary artery. The remaining branches generally parallel one another and pass toward, but do not reach, the apex. At the acute or right margin of the right ventricle a fairly large branch, the right marginal artery, leaves the right coronary artery and extends down the acute margin about four fifths of the distance toward the apex. The right coronary artery still proceeds in the coronary sulcus and on the posterior surface of the heart gives off one or more branches which may course toward the apex or may go diagonally toward and end in the posterior part of the interventricular septum. When the right coronary artery reaches the posterior interventricular sulcus, it generally gives off a large branch which travels along the sulcus for about three fifths of the distance from the coronary sulcus

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to the apex, where it generally turns into the interventricular septum. This branch, which may be called the posterior descending artery, gives off many branches to the posterior third of the septum. The right coronary artery generally continues in the coronary sulcus, crossing the posterior interventricular sulcus to reach the posterior surface of the left ventricle. Here it ends by dividing into two or more branches, which extend from the coronary sulcus for about three fifths of the distance toward the apex. These vessels usually do not extend to the left beyond a line from one half to two thirds of the distance from the posterior interventricular sulcus to the obtuse or left margin of the heart. Figure 1 shows the portion of the posterior surface of the heart usually supplied by the right coronary artery.

The left coronary artery arises from the left posterior sinus of Valsalva and almost immediately divides into two main branches. The larger of these branches, the anterior descending artery, proceeds down the anterior interventricular sulcus to the apex, and from this point it generally extends on to the posterior surface of the heart, coursing up the posterior interventricular sulcus usually from a fourth to a third of the distance toward the base of the ventricles. At its termination its branches supply the posterior surface of the apex of both ventricles. As the artery passes down the anterior surface of the heart, it gives off a few small branches which proceed for a short distance to the right to reach the anterior border of the right ventricle. Several large branches leave the anterior descending artery passing diagonally downward and to the left to supply the anterior surface of the left ventricle and the lower portion of the obtuse margin. These arteries have been called the accessory anterior descending arteries by Spalteholz¹ and the rami marginalis by Gross.² The anterior descending artery also has many large branches which leave its inferior surface and pass into and supply the anterior two thirds of the interventricular septum.

The other main division of the left coronary artery is known as its circumflex branch. It arises near the origin of the left coronary artery and courses immediately to the left, following the coronary sulcus for a variable distance. It generally passes around the obtuse or left margin of the heart, where it leaves the coronary sulcus to reach and supply the left third or left half of the posterior surface of the basal three fifths of the left ventricle. Some of the rami marginalis (or accessory anterior descending arteries) may take origin from this vessel instead of from the anterior descending artery.

1. Spalteholz, W.: *Die Arterien der Herzwand*, Leipzig, S. Hirzel, 1924.

2. Gross, Louis: *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B. Hoeber, 1921.

In the average normal heart, the left coronary artery supplies the entire anterior surface of the left ventricle, the adjacent third of the anterior surface of the right ventricle, the apex of both ventricles, all of the interventricular septum at the apex, the anterior two thirds of the remainder of the septum and the left half of the posterior surface

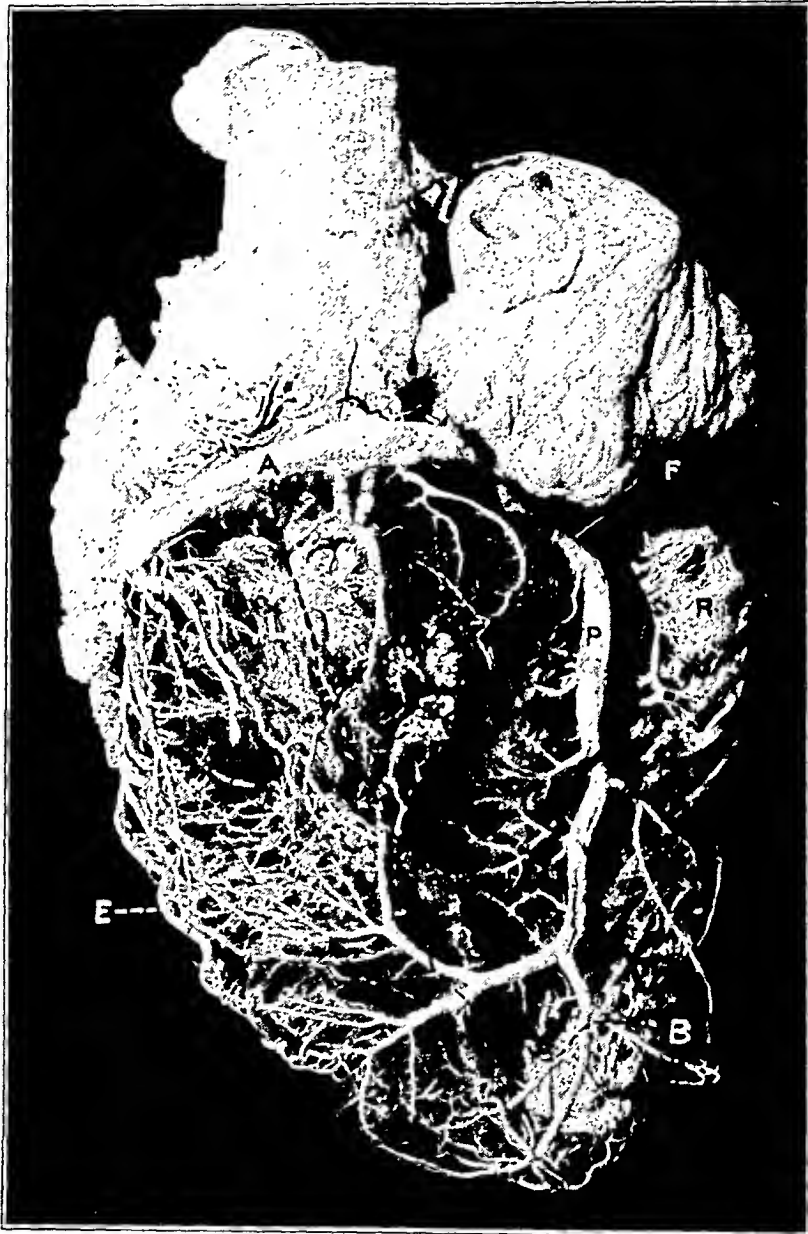


Fig. 1.—Posterior view of heart prepared by celluloid-corrosion method, from a man, aged 42. The vascular preponderance of the left ventricle is evident. *R*, right ventricle; *L*, left ventricle; *E*, left coronary artery; *F*, right coronary artery; *P*, posterior interventricular vein. Broken line from *A* to *B* separates the portions of the heart supplied by the right coronary artery from the portions supplied by the left. This represents almost the average normal line of separation, except in the base of the left ventricle, where the circumflex branch of the left coronary artery supplies a little more of the posterior surface than is usual.

of the left ventricle. It also supplies the anterior papillary muscles and the lower portion of the posterior papillary muscles of the left ventricle as well as most of the anterior papillary muscles of the right ventricle.

The right coronary artery usually supplies two thirds of the anterior surface and all of the posterior surface of the right ventricle, except the apex. In addition, it generally supplies the posterior third of the interventricular septum (except at the apex) and the adjacent half of the basal three fifths of the posterior surface of the left ventricle. The right coronary artery also supplies the posterior papillary muscles, a small portion of the anterior papillary muscles of the right ventricle, and generally the upper portion of the posterior papillary muscles of the left ventricle.

Variations in the Distribution of the Coronary Arteries.—According to Spalteholz, Banchi (1904) found the coronary arteries to have their average normal distribution, approximately as has been described, in 80 per cent of his ninety-two cases. However, there are several definite and comparatively common variations from the average distribution of the coronary arteries. The posterior surface of the left ventricle and the posterior part of the interventricular septum are the regions chiefly affected by these variations.

In four of approximately forty hearts which I have injected, the circumflex branch of the left coronary artery took on unusual significance and resembled the distribution, as usually described, of the corresponding artery in the dog.³ Banchi found this variation in 10 per cent of the hearts of his series, and Gross in 8 per cent of his. In such hearts, the circumflex artery continues in the coronary sulcus, passes across the entire anterior and posterior surfaces of the left side of the heart to reach the posterior interventricular sulcus, turns down it and courses about three fifths of the distance toward the apex. When the artery passes down the interventricular sulcus, it becomes the posterior descending artery, which is usually a branch of the right coronary artery. The posterior descending artery generally gives off a few small branches to the adjacent portion of the posterior surface of the right ventricle. Thus, not only the whole posterior surface of the left ventricle, but also the entire interventricular septum, and sometimes some of the posterior surface of the right ventricle, as in figure 2, are supplied by the left coronary artery. This is compensated for by the right coronary artery being smaller than usual and generally not supplying any of the septum and perhaps only a portion of the posterior surface of the right ventricle. The distribution of the right coronary artery in the anterior surface of the right ventricle generally is unchanged in the presence of this variation in its distribution elsewhere. Sometimes

3. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart: A Modification of the Celluloid and Corrosion Technic, Arch. Int. Med. 42:846 (Dec.) 1928. Gross (footnote 2).

both the right and the left coronary arteries supply the basal portion of the posterior part of the interventricular septum.

Spalteholz also published a diagram which was based on Banchi's work and which showed the right coronary artery supplying more of the posterior surface of the left ventricle than in the average heart. Banchi found that the left ventricular branches of the right coronary artery reached to the left almost as far as the obtuse margin in about 17 per cent of the hearts examined, and well around the obtuse margin and on to the anterior surface of the left ventricle in 5 per cent. My series of cases is too small to attempt to establish the frequency with

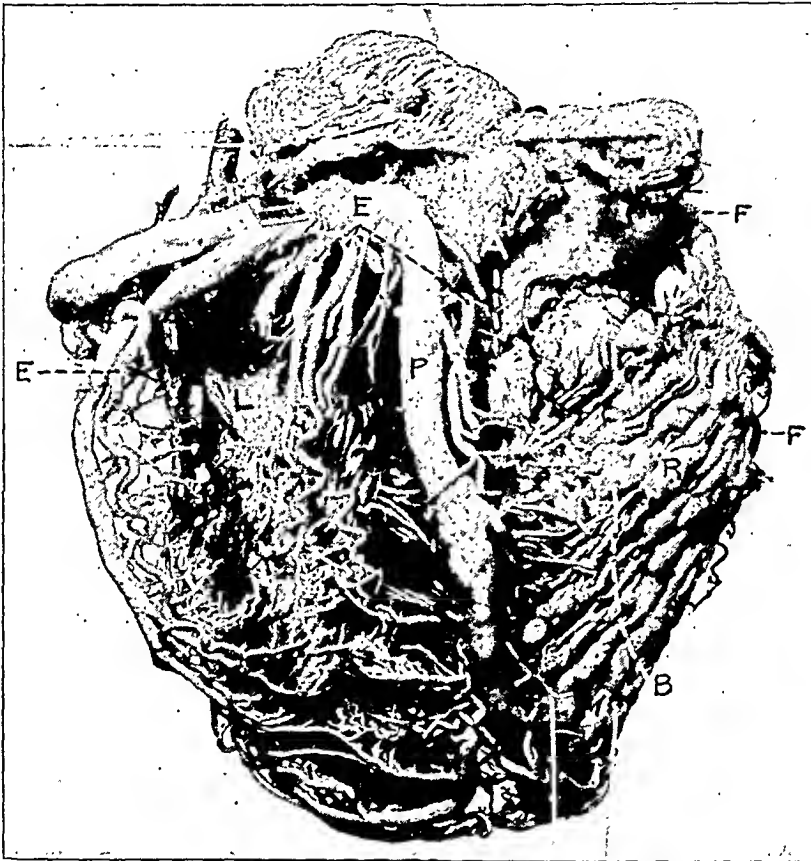


Fig. 2.—Heart, prepared by celluloid-corrosion method, from a woman, aged 55. The left coronary artery supplies the entire posterior surface of the left ventricle and a portion of the posterior surface of the right ventricle. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein. The broken line from *A* to *B* separates portions of the right ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

which this type of distribution of the coronary circulation occurs. However, I have been able to verify the existence of these variations in the amount of the posterior surface of the left ventricle supplied by the right coronary artery (fig. 3).

The extent to which the posterior descending branch of the right coronary artery tends to extend toward the apex of the heart shows a

significant variation in the consideration of infarction. It was stated that, in the average heart, the branches of the right coronary artery extend about three fifths of the distance from the coronary sulcus to the apex, and that the remaining apical portion of the posterior surface of the two ventricles is supplied by the anterior descending branch of the left coronary artery. At times, the posterior descending artery

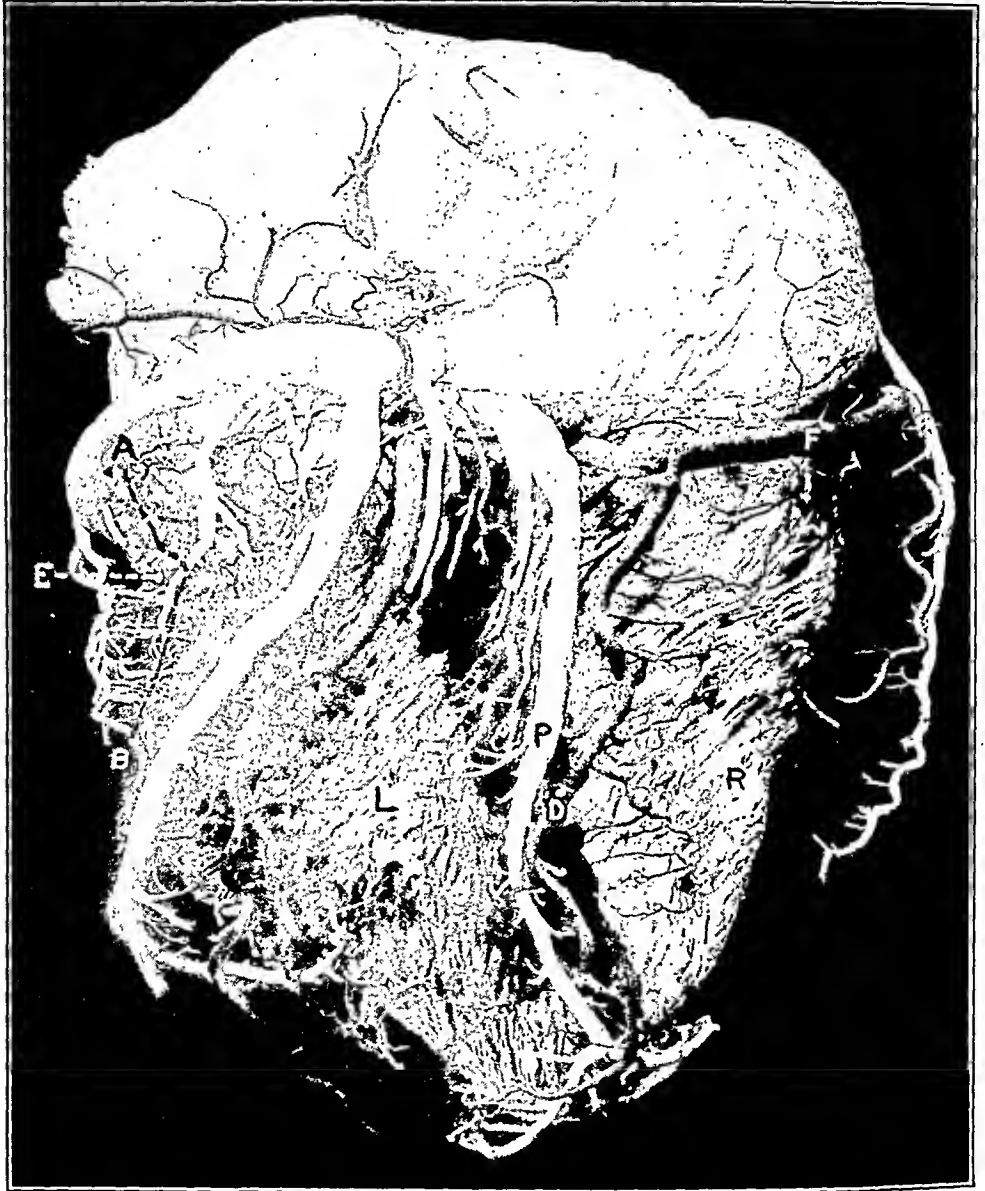


Fig. 3.—Posterior view of heart prepared by celluloid-corrosion method. The right coronary artery supplies the entire posterior surface of the left ventricle and the apex. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein; *D*, posterior descending artery (right coronary); broken line from *A* to *B* separates parts of left ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

extends to and supplies the apex of the heart. This arrangement usually is associated with increased length of the posterior arteries of the left ventricle (right coronary branches) so that they also reach to or nearly to the apex (fig. 3). In the presence of this variation, the apex and almost the entire posterior surface of the left ventricle receive their blood supply from the right coronary artery.

The variations in the coronary arteries which have been mentioned are of the more extreme types. It must be understood that variations which are similar but of lesser degree also exist. In fact, slight variations in the coronary arteries are so common that a heart showing the entire average distribution is rarely encountered.

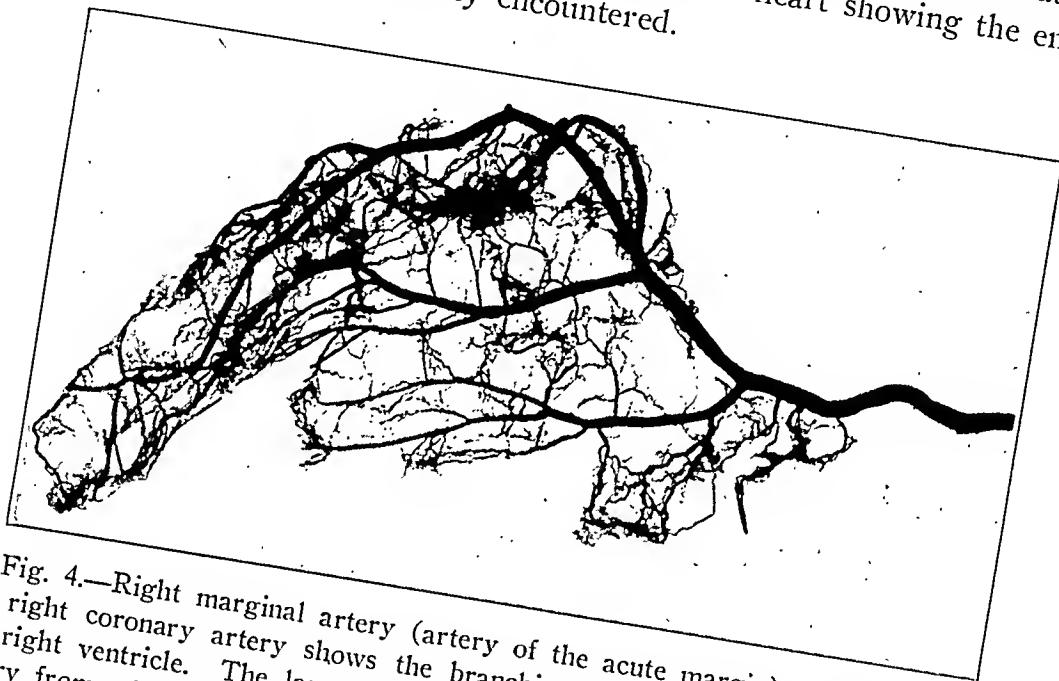


Fig. 4.—Right marginal artery (artery of the acute margin). This branch of the right coronary artery shows the branching characteristic of the arteries of the right ventricle. The large and small branches lie in the same plane as the artery from which they arise ($\times 2$).

ARCHITECTURAL DIFFERENCES IN THE ARTERIES SUPPLYING THE RIGHT AND LEFT VENTRICLES

Structure of Coronary Arteries.—It has not been emphasized sufficiently that there is a definite difference in the manner of branching of the arteries supplying the right and left ventricles. The deep branches were found by Gross to leave at right angles and to pass straight through the wall of the heart until they reached the subendocardial tissue, where they divided into a mass of fine branches. However, he did not make any distinction between the method of arborization of the vessels of the right and left ventricles.

As a rule, the smaller branches of the right coronary artery supplying the right ventricle spread out over the heart in the same general plane as the subdivisions from which they arise. This type of branch-

ing is illustrated in figure 4. It is characteristic of the normal right ventricle. When the right ventricle is enormously thickened, some of the branches have a tendency to go deep but this is usually under pathologic conditions. An illustration of a heart, in which this condition is present, accompanies another paper.⁴ The wall of the left ventricle is much thicker than that of the right in the normal adult heart. The main branches that supply the left ventricle, whether they originate in the right or left coronary artery, course along the surface of the heart just beneath the epicardium (fig. 5 *a*). The vessels leaving these branches do not spread out in the same general plane as the artery from which they arise. Instead, they leave at right

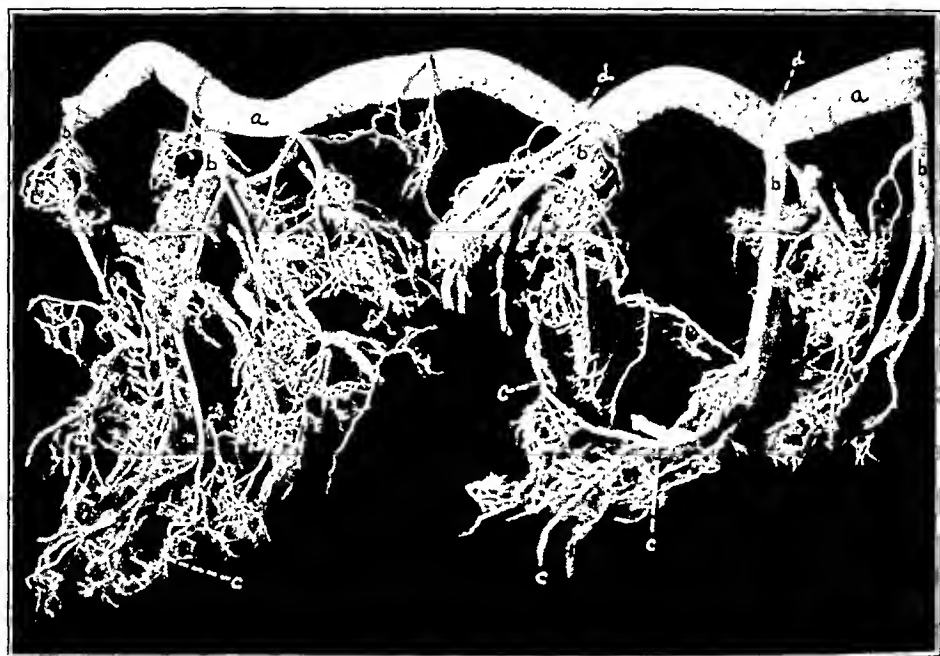


Fig. 5.—Left coronary artery from the left ventricle. *a*, large branch following just beneath the epicardium; *b*, branches leaving at right angles from the inferior surface of *a*, passing directly through the myocardium and having an anchoring effect on *a*; *c*, large and small subendocardial branches; *d*, kinking and constrictions at point at which deep vessels leave to penetrate myocardium ($\times 6$).

angles from the inferior surface of the larger vessel, and penetrate directly through the myocardium (fig. 5 *b*), giving off few branches until they reach the endocardium, where they turn at a sharp angle and end in a mass of fine arterioles (fig. 5 *c*). In figure 5 is illustrated a branch of the left coronary artery from the wall of the left ventricle. It may be seen that the portion of the right coronary artery supplying the left ventricle (fig. 6) has a similar type of branching. When a

4. Whitten, M. B.: A Comparison of the Blood Supply of the Right and Left Ventricles in Childhood, *Arch. Int. Med.* **45**:46 (Jan.) 1930.

branch of the right coronary artery in the left ventricle (fig. 6) is compared with a branch of the right coronary artery in the right ventricle (fig. 4), a marked difference in the structure of the same vessel in the two ventricles is observed.

Theoretical Consideration.—Branches that leave the surface vessels at right angles to penetrate the myocardium (figs. 5 *b* and 6) and are

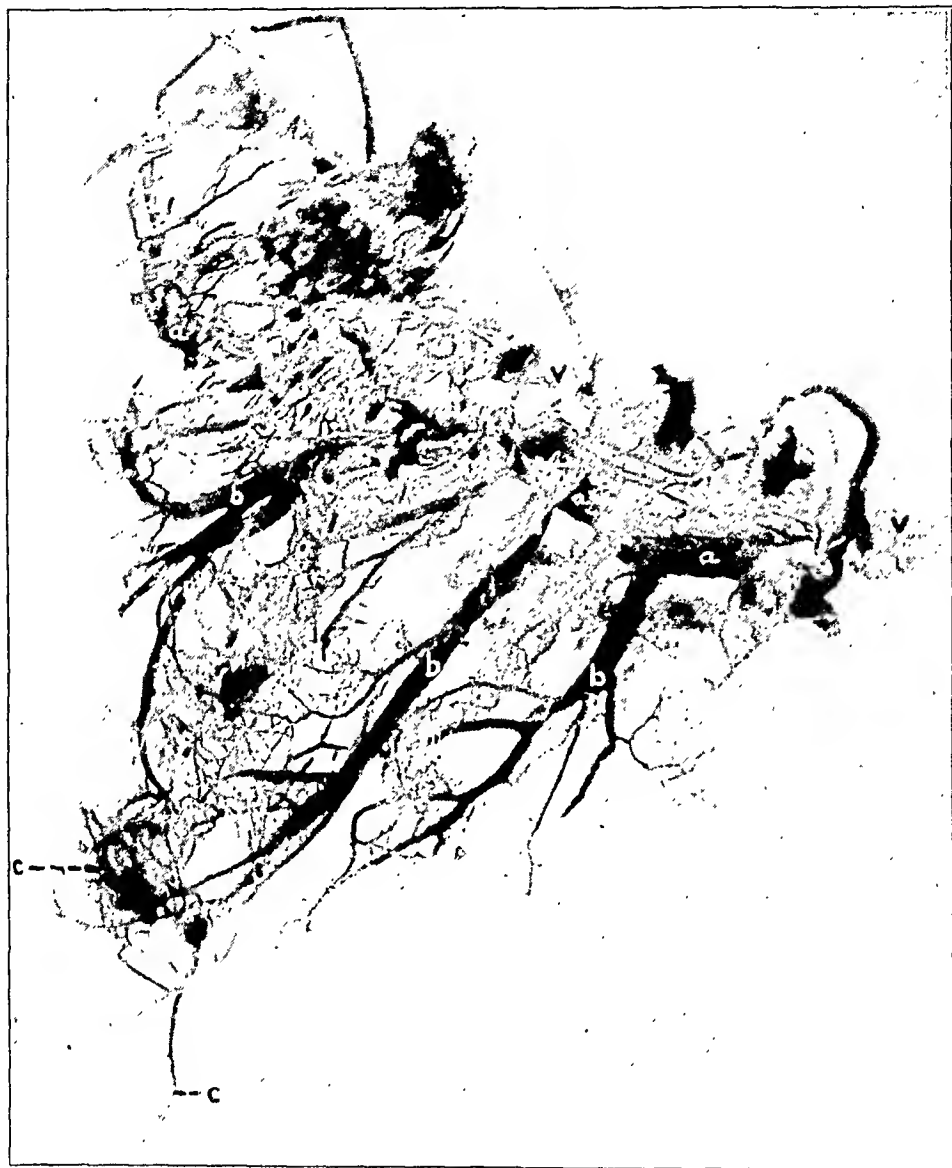


Fig. 6.—Branch of right coronary artery from left ventricle. *a*, branch following just beneath the epicardium; *b*, branches leaving at right angles from the inferior surface of *a*, passing directly through the myocardium and having an anchoring effect on *a*; *c*, large and small subendocardial branches; *v*, vein accompanying artery ($\times 6$).

characteristic of the left ventricle appear to immobilize the main arteries. This immobilization, or anchoring, of a main vessel appears to augment its tortuosities, possibly leading to kinking or constriction, with consequent diminution of its lumen at the point of narrowing.

Besides the relative absence of anchorage by deep branches, the right coronary artery, as it swings around the right side of the heart, describes an almost complete semicircle. It is suggested that this, also, is a protection to this part of the right coronary artery; if this vessel becomes sclerosed, it may not become very tortuous because it is free to describe a larger arc. Obviously, however, this mobility is not shared by the portion of the right coronary artery which supplies the left ventricle and the posterior part of the interventricular septum.

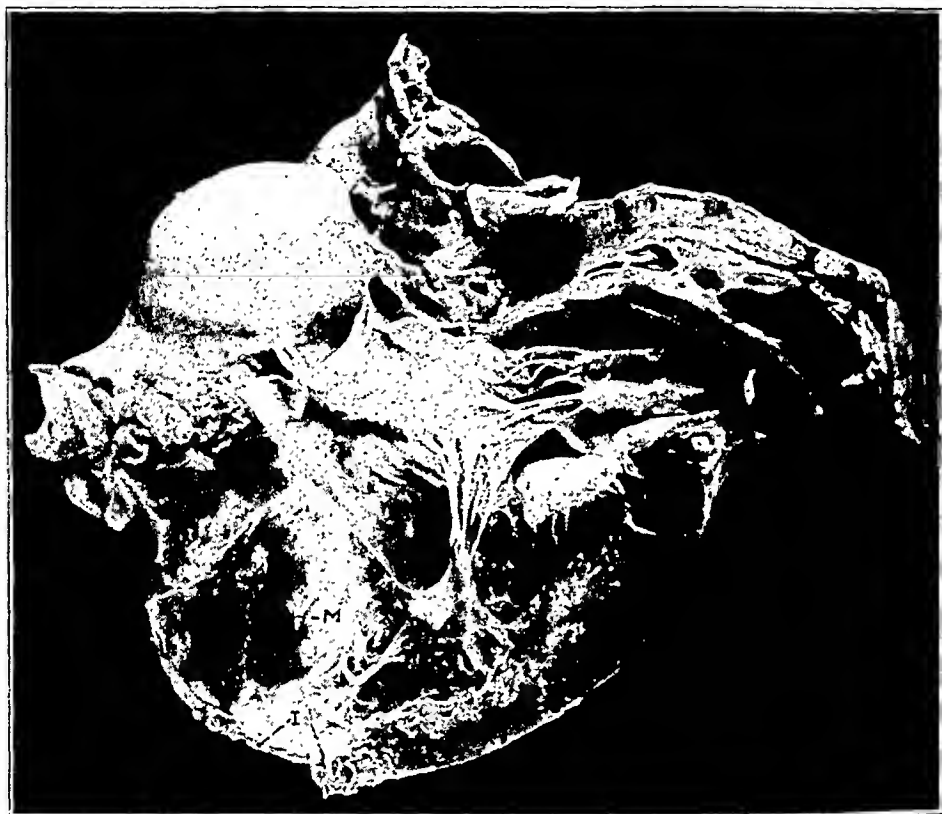


Fig. 7.—Massive infarction of the anterior wall of the left ventricle probably produced by occlusion of one of the larger arteries. There is marked thinning of the ventricular wall. A mural thrombus is present. *M*, mural thrombus; *A*, normal heart muscle above the region of infarction; *I*, old infarct with marked thinning of the ventricular wall.

THE APPARENT RELATIONSHIP OF THE DISTRIBUTION AND STRUCTURE OF THE CORONARY ARTERIES TO MYOCARDIAL INFARCTION

A number of anatomic observations concerning the coronary arteries have been mentioned here. Some of these factors play a part in the production and localization of myocardial infarction.

In a study of infarction in hearts at necropsy, it was noted that three distinct types were present. In some of the hearts a rather large zone

of destruction and fibrosis was found, caused, it was believed, by the occlusion of one of the larger branches of the coronary arteries (fig. 5 *a*). Infarction of this type produced the most extensive lesion found and often was associated with marked thinning of the ventricular wall (fig. 7).

In a number of hearts, a different type of infarction was noted. Those infarctions were recognized generally because of the depression



Fig. 8.—Depression on the posterior surface of the left ventricle due to chronic infarction and resultant contraction of cardiac wall in a localized region. All indentations in the surface of the heart, such as this one, should be incised (fig. 10) at the postmortem examination, or localized infarctions will escape attention. *D*, depression on heart surface.

that they produced on the surface of the ventricle (fig. 8). They were associated with the later fibrous stages of infarction. They were likely to be considered as examples of epicardial thickening and likely not to be recognized at postmortem examination. However, they could be distinguished readily from the "soldier's spots" by the definite indentation they produced in the surface of the heart. If the depressed area was 5 mm. or more in diameter, chronic infarction almost invariably was

found on cutting through the myocardium at that point (fig. 9). This type of infarction seemed to be due to the plugging of one or more of the deep branches (fig. 5 *b*) that leave the surface artery at right angles and penetrate through the myocardium. In this type of lesion the infarction generally extended almost through the myocardium in a zone that corresponded fairly well with the depression on the surface; that is, the chronically infarcted region seemed to have a distribution that roughly paralleled one of the perpendicular branches that penetrated the myocardium. A localized infarction, which passed almost completely through the ventricular wall, was produced. It was believed that the contraction of the resulting scar tissue, in which the longest diameter was perpendicular to the surface of the heart, was responsible for the depressions that were observed in old infarctions of this type.

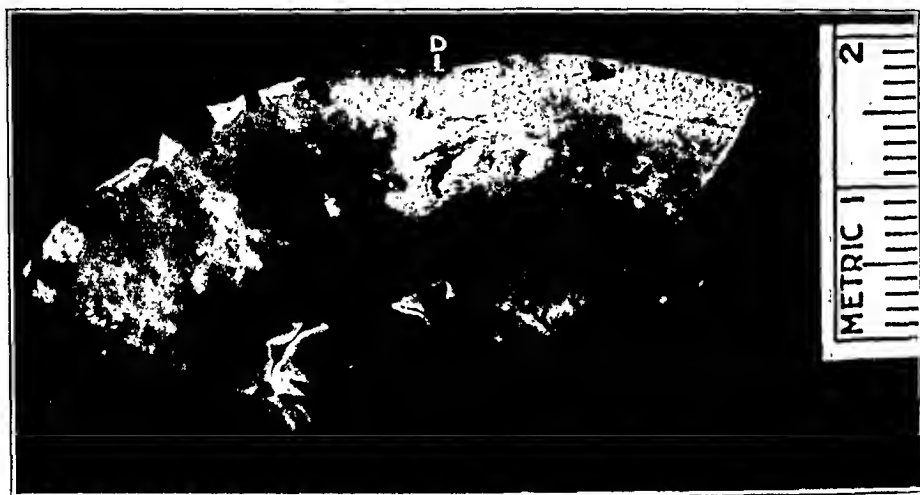


Fig. 9.—A cross-section of the posterior surface of the left ventricle, cut through the depression on the surface of the heart seen in figure 7. The white region of fibrosis deep to the depression is seen; *D*, depression on heart surface.

Karsner⁵ may have been referring to this type of infarction when, in describing the pathologic features of infarction, he stated, "The infarct is generally conical in shape with the apex near the epicardium and the base toward the endocardium."

In a third group of hearts the observed infarction was confined to the endocardial third or fourth of the ventricular wall. In infarction of this type (fig. 10), the longest direction of the fibrous zone of replacement was parallel to the endocardium, and the infarction, although it might spread over a considerable area, involved only the subendocardial portions of the wall of the heart. A lesion of this type, although at times it caused some thinning of the ventricular wall, did not produce

5. Karsner, H. T.: *Human Pathology*, Philadelphia, J. B. Lippincott Company, p. 440, 1926.

indentations of the ventricular surface, as seen in the previous type of infarction, because the fibrotic zone was near to and parallel with the endocardium instead of in a plane perpendicular with the surface of the heart. It was believed that this type of infarction was produced by the occlusion of one or more of the larger subendocardial branches

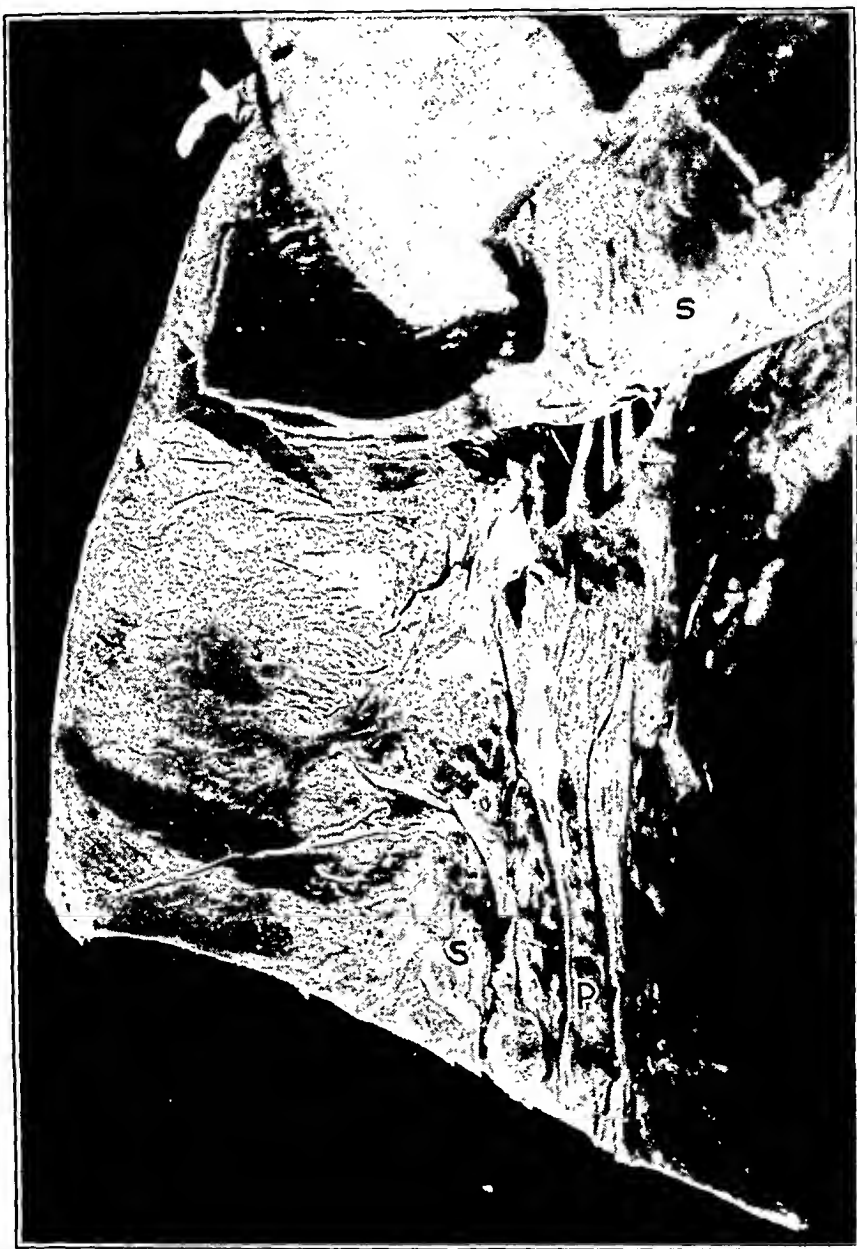


Fig. 10.—Section through the wall of the left ventricle showing old infarction confined to the subendocardial portion of the cardiac wall and the papillary bundles. *S*, subendocardial infarction; *P*, infarction of the papillary bundles.

(fig. 5 *c*) that course often for a considerable distance in the subendocardial musculature, usually in relation to the columnae carnae or papillary bundles.⁶ This is probably the type of infarction observed

6. The part played by the anastomosis or the thebesian veins in the prevention of or recovery from infarction has not been studied in connection with this paper.

by Oppenheimer and Rothschild⁷ in their study of arborization block, for they concluded that infarction most frequently was subendocardial.

The frequency with which infarction occurs in the posterior surface of the left ventricle and the infrequency with which it occurs in the right ventricle recently have been emphasized by Parkinson and Bedford. Barnes and Whitten⁸ pointed out that in forty-seven cases of myocardial infarction, proved by necropsy, the left ventricle was involved in every case. In thirty-six cases there was infarction in portions of the left ventricle supplied by the left coronary artery, and in twenty-two cases the infarction involved portions of the left ventricle supplied by the right coronary artery. In only four cases was there any appreciable infarction in the right ventricle. In each of these four cases there was involvement also of the posterior surface of the left ventricle which was much more extensive than that occurring in the right, but was confined to the distribution of the right coronary artery.

The structural differences in the arteries supplying the right and the left ventricles are so strikingly at variance that it seems that they may play the major part in the localization of infarction. It has been demonstrated previously that the branches of the arteries of the right ventricle spread practically in the same general plane as that of the artery from which they arise. It has been shown, likewise, that the branches of the arteries of the left ventricle leave the main trunks at right angles and penetrate directly through the myocardium. That these branches leaving at right angles (fig. 5 *b*) have a tendency to immobilize the larger vessels and to cause the tortuosities of the vessels to produce angulation and kinks, with narrowing of the lumen of the main artery, also has been mentioned. This, together with the fact that intimal proliferation and sclerosis of the coronary arteries often is most marked at the points at which these vessels (fig. 5 *b*) leave the main trunks, seems to suggest that the structural differences in the arteries of the two ventricles are closely related to the incidence of infarction in their walls.

It was found that infarction produced in the left ventricle by a lesion of the left coronary artery was much more frequent as a result of disease of the anterior descending artery than of the circumflex branch. If one were to attempt to explain this on an anatomic basis, some difficulty would be encountered, because both arteries supply the left ventricle. However, the anterior descending artery, throughout its

7. Oppenheimer, B. S., and Rothschild, M. A.: *Electrocardiographic Changes Associated with Myocardial Involvement with Special Reference to Prognosis*, J. A. M. A. **69**:429 (Aug. 11) 1917.

8. Barnes, A. R., and Whitten, M. B.: *A Study of the R-T Interval in Myocardial Infarction*, Am. Heart J. **5**:142 (Dec.) 1929.

entire length, has many deep branches leaving it at right angles, for this vessel supplies two thirds of the interventricular septum. On the contrary, the first portion of the circumflex artery follows the coronary sulcus and is really above the ventricle itself. Consequently, this portion of the circumflex artery has few deep branches leaving at right angles from its inferior surface, but instead, has a number of large surface branches extending in the direction of the apex. The main branches of the circumflex artery, however, and the circumflex artery itself, as soon as it leaves the coronary sulcus, give off many deep branches which leave at right angles to penetrate the myocardium. It is possible, then, that the circumflex artery is spared somewhat because its first, or supraventricular, portion is not anchored as securely by deep branches as is the entire anterior descending artery.

Infarction caused by occlusion of the anterior descending artery or its branches was most commonly found to involve the apex and the lower half of the anterior surface of the left ventricle as well as a portion of the anterior part of the interventricular septum. The papillary bundles of the left ventricle sometimes were involved. The right ventricle, where it was supplied by the left coronary artery, was generally spared. The infarction produced by occlusion of the circumflex artery or its branches usually involved the obtuse margin of the left ventricle about half way from base to apex, but infarction from a lesion of this artery might also be found at the base and occasionally quite near to the apex. In one heart, infarction of the posterior surface of the left ventricle was produced by occlusion of the circumflex artery. In this heart the circumflex artery was similar to that illustrated in figure 2, and it supplied the posterior surface of the left ventricle and the posterior part of the interventricular septum.

Infarction in the posterior surface of the left ventricle, in the distribution of the right coronary artery, is much more common than has been supposed. There are a number of reasons why infarction in this region has been overlooked so frequently. In the first place, it has been believed for some time that the anterior descending branch of the left coronary artery is the vessel usually involved. In fact, this artery has been named by some "the artery of coronary occlusion" and "the artery of sudden death." No one has ever emphasized the fact that the right coronary artery, where it supplies the left ventricle, has a different type of branching from that which it has in the right ventricle, and is therefore especially vulnerable. Furthermore, the frequency with which occlusion, with resulting infarction, occurs in more than one coronary artery also has escaped attention. Consequently, when infarction has been found in the anterior surface of the left ventricle, often careful search has not been made for infarction in the distribution of the right coronary

artery. Also, infarction at the apex generally has been assumed to have been produced by a lesion in the anterior descending artery, and it has not been recognized that infarction in this situation may be produced by occlusion of the right coronary artery when that vessel, as occasionally happens, extends to the posterior surface of the apex. Many infarctions in the posterior surface of the left ventricle are overlooked if the examination of the heart does not include an incision through the posterior surface of the left ventricle. Recent infarction may not be recognized grossly, and may be overlooked microscopically if sections are not taken from the regions most frequently infarcted. Also the importance of an examination of all indentations of the surface of the heart, such as the one illustrated in figure 8, has not been sufficiently emphasized. If these depressions are 5 mm. or more in diameter they should be cut into as they often represent the contracted scar of an old infarct. Finally, it has not been known that infarction of the posterior surface of the left ventricle produces electrocardiographic changes distinctly different from those of infarction of the anterior surface of the left ventricle.

When infarction occurred in the region supplied by the right coronary artery it was situated almost always in the posterior part of the left ventricle. The site of this infarct naturally varied somewhat with the extent to which the posterior surface of the left ventricle was supplied by the right coronary artery. The infarct often was found to lie near the termination of the left ventricular branches of the right coronary artery. If the right coronary artery extended to the obtuse margin, or to the apex, a portion of the infarction might occur in the region usually supplied by the circumflex or by the anterior descending branch of the left coronary artery. The infarct more frequently involved the posterior wall of the left ventricle than the interventricular septum. Just why the posterior descending artery should be less frequently involved than the left ventricular branches of the right coronary artery is difficult to explain.

It was suggested that occlusion occurred as frequently as it does in the portion of the right coronary artery that supplies the left ventricle because in the left ventricle the right coronary artery takes on a type of branching that differs definitely from that which it possesses in the right ventricle. Furthermore, in the left ventricle, the branches of the right coronary artery are similar to the branches of the left coronary artery which supply the left ventricle, and probably are equally liable to occlusion.

Grossly recognizable infarction was not found in the right ventricle except in four of forty-seven cases of myocardial infarction. In each of the four hearts, there was much more infarction in the adjacent portions of the left ventricle and interventricular septum, whereas the infarction

of the right ventricle was in the portion adjacent to the septum, and was minimal in amount. Infarction in the right ventricle, because of its association with extensive infarction in the adjacent portion of the left ventricle, usually was found in the presence of an occlusion of a large branch of the right coronary artery. The vessel most commonly involved was the posterior descending artery, which supplies the posterior portion of the interventricular septum and a portion of the adjoining right and left ventricles.

Evidence of infarction was not found on the anterior surface of the right ventricle in association with occlusion of the anterior descending artery, even though the septum was extensively involved. The small branches which extend to the anterior surface of the right ventricle, from the anterior descending branch of the left coronary artery, evidently receive sufficient anastomosis from the anterior arteries of the right ventricle (right coronary artery) to sustain this portion of the myocardium.

The declaration of Gross that with advancing age there is increasing decline and failure of the right side of the heart, and that this probably is due to changes in the right coronary artery, has been mentioned. The present study of the circulation indicates that the portion of the right coronary artery which supplies the left ventricle keeps pace, in its vascular development, with the left coronary artery in successive decades. Furthermore, it has not been possible to demonstrate the impoverishment of the circulation in the right ventricle which was found by Gross. In fact, in a heart in which there was hypertrophy of the right ventricle there was a definite increase in the vascularity of that ventricle. Also, when the incidence of infarction is considered, the blood vessels in the right ventricle are certainly less vulnerable, and hence more efficient, than the circulation in the left ventricle. Therefore, the evidence indicates that, although the right ventricle has fewer blood vessels than the left, it is much more likely to receive an adequate blood supply even with advancing years.

The recent work of Barnes and Whitten indicates that infarction of the posterior surface of the left ventricle in the region usually supplied by the right coronary artery produces electrocardiographic changes which are distinctly different and opposed to those produced by infarction in the anterior surface of the left ventricle in the region supplied by the left coronary artery. It is possible to recognize the portion of the left ventricle infarcted, and on the basis of the average blood supply to the region involved, to predict with a high degree of accuracy the coronary artery involved. On the basis of these observations it was suggested that in its electrical effects on the T wave the posterior surface of the left ventricle acts oppositely to the anterior portion. It is interesting that the line of division between these two opposing regions

corresponds closely with the plane separating the portion of the left ventricle supplied in the average heart by the right coronary artery from the region supplied by the left.

SUMMARY AND CONCLUSIONS

1. The deep branches of the arteries of the left ventricle leave at right angles and pass directly through the myocardium. The branches of the arteries of the right ventricle spread out in practically the same plane as the larger artery from which they arise.

2. Three distinct types of lesions are produced by infarction involving the left ventricle. The nature of the infarction depends on the site of the occlusion.

3. The fact that the injury in infarction is almost always to the left ventricle, whereas the right ventricle rarely is involved, seems to depend on the differences in the anatomic structure of the arteries of the two ventricles.

4. Infarction in the posterior surface of the left ventricle is much more common than has been heretofore recognized. Infarction at the apex may be due occasionally to occlusion of the right coronary artery.

5. It is suggested that the position of the first part of the circumflex branch of the left coronary artery, while it is in the coronary sulcus and above the ventricle, is a factor in making it less liable to occlusion than the anterior descending artery.

6. Infarction in the right ventricle was found only in connection with massive infarction of the left ventricle and usually was minimal in amount.

7. The right ventricle, although it appears to be less vascular than the left, is not believed to be especially predisposed to failure with age. In fact, the left ventricle is found to be the one to fail most frequently from arterial insufficiency.

THE CLINICAL ASPECT OF APUTRID PULMONARY NECROSIS *

LEO KESSEL, M.D.

NEW YORK

During the past three years I have encountered a condition arising in the course of lobar pneumonia, which at first I was unable to explain. Usually at the time of resolution, a roentgenogram of the chest would show a perfectly definite cavity which had produced no symptoms. Repeated roentgenologic examinations would reveal the fact that these cavities decreased in size, and at the end of about two weeks they would have disappeared.

REVIEW OF THE LITERATURE

I was unable to find any data in the literature which threw light on this subject until I made a search through the literature pertaining to the pathology of pneumonia. From a study of this literature it became apparent that the clinical aspect of the condition, which was subsequently called "aputrid pulmonary necrosis" by Kaufmann,¹ had never been described. In 1907, Rosenthal² of Berlin reviewed the literature and reported one case. He stated that beside the ordinary terminations of lobar pneumonia in abscess, gangrene and carnification, there also occasionally arises a form known as sequestration. This sequestration is a necrosis resulting from a thrombosis of the vessels supplying the affected part of the lung. The cause of the anemic infarction is dependent on the inability to form a collateral circulation, and this in turn is due to multiple thrombi, compression of the blood vessels, particularly the capillaries, by the pneumonic exudate, obliteration of the capillaries by the growth of interstitial connective tissue, anthracosis and weakening of the heart, particularly of the right side. The pathologic features of this condition have been mentioned by Kaufmann,¹ Büdinger³ and Lebert,⁴ and individual cases have been reported by Brinckmann,⁵

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* From the Medical Service of the Mount Sinai Hospital.

1. Kaufmann: *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, G. Reimer, 1904, pp. 103, 226 and 238.

2. Rosenthal, Theodor: *Ueber den Ausgang der fibrinösen Pneumonie in aputride anämische Nekrose*, Berlin, G. Schade, 1907.

3. Büdinger: *Ueber Lungensequester*, München. med. Wchnschr. **18**:1874, 1904.

4. Lebert: *Traité d'anatomie pathologique*, Paris, J. B. Baillière & fils, 1857, vol. 1, p. 738; *Klinik der Brustkrankheiten*, Tübingen, H. Laupp, vol. 1, p. 802.

5. Brinckmann: *Ein Fall von Sequestrierung der Lunge nach Pneumonie*, Diss., Kiel, 1897.

Henoch⁶ and Kühn.⁷ Lauche⁸ reported two cases, in one of which necrotic sequestrated lung tissue was found attached to the surrounding lung by a stalk containing the thrombosed vessel. Aufrecht⁹ reported a case in which a necrotic sequestrum was removed at operation, after having perforated the pleural cavity. One case was also reported by Auguste-Jean Thomas,¹⁰ who gave some review of the literature. The anemic infarction in this case was discovered at autopsy. Cagnetto¹¹ mentioned the occurrence of anemic necrosis in the course of lobar pneumonia, and stated that this was seen most commonly in the stage of hepatization, and in the region of the margins of the lung, where the blood flow in the capillaries is slower, and where the collateral circulation is established with greater difficulty. Cagnetto¹¹ agreed that the development of an anemic infarction was favored by the state of hepatization in the lung with its compression of the capillary bed, previous atheromatous conditions in the pulmonary vessels and emphysema. According to this author the anemic infarctions occurred most commonly in elderly people.

The literature therefore revealed the fact that the condition had been described from a pathologic standpoint, that it had never been suspected clinically, and that therefore none of the patients had ever had a roentgenogram taken of the lungs.

REPORT OF CASES

CASE 1.—The first patient seen by me who disclosed this condition was a Russian operator, B. D., aged 24, who was admitted to the hospital in March, 1926. There were a few indefinite physical signs posteriorly over the lower lobe of the right lung. The temperature ranged between 100 and 102 F. The roentgenogram taken on March 15 showed a pneumonic infiltration in this area, and within this an oval cavity about 2 inches (5 cm.) in diameter, showing a fluid level. It was thought that this represented an abscess of the lung. The hemoglobin was 96 per cent; the white cell count was 19,600, with 74 per cent polymorphonuclears. Bronchoscopic examination failed to reveal an abscess, and nothing abnormal was found in the bronchi other than a moderate narrowing of the opening of the branch of the middle lobe with a congestion of the main bronchus surrounding this opening. The whole condition remained obscure to me, because clinically there

6. Henoch: *Vorlesungen über Kinderkrankheiten*, Berlin, A. Hirschwald, 1903, p. 817.

7. Kühn: *Ueber den Ausgang der kindlich kroupösen Pneumonie in Lungen-sequestrirung*, *Arch. f. Kinderh.* **37**:278, 1903.

8. Lauche, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, vol. 3, pt. 1, p. 758.

9. Aufrecht: *Die Lungenentzündungen*, in Nothnagel: *Spezieller Pathologie und Therapie*, Vienna, Alfred Hölder, 1890, vol. 15, p. 114.

10. Thomas, Auguste-Jean: *Un cas d'infarctus anémique du poumon*, Geneva, Eausanne, 1913.

11. Cagnetto, G.: *Della necrosi anemica, a focolai, come esito raro della pneumonite crupale*, *Pathologica* **3**:532, 1911; *Centralbl. f. allg. Path. u. path. Anat.* **23**:840, 1912.

was no evidence of an abscess of the lung, there was no etiologic factor, and on bronchoscopic examination, there was no confirmation that there was an abscess of the lung; however, the roentgenogram definitely showed an abscess to be present. The course of the resolving pneumonia was normal; the temperature came down to under 100 F.; the physical signs remained the same, and neither the cough nor the expectoration was in any way remarkable. The second roentgenogram, taken on March 20, showed a marked decrease in the size of the pneumonic area previously reported in the lower lobe of the right lung, and the cavity was half its previous size. On April 1, examination of the chest showed an almost complete disappearance of the infiltration previously reported in the right lung, and the cavity had also disappeared. On April 15, a roentgenogram showed complete disappearance of the infiltration previously reported, so that here there was a resolving pneumonia in a young woman who presented no unusual clinical phe-

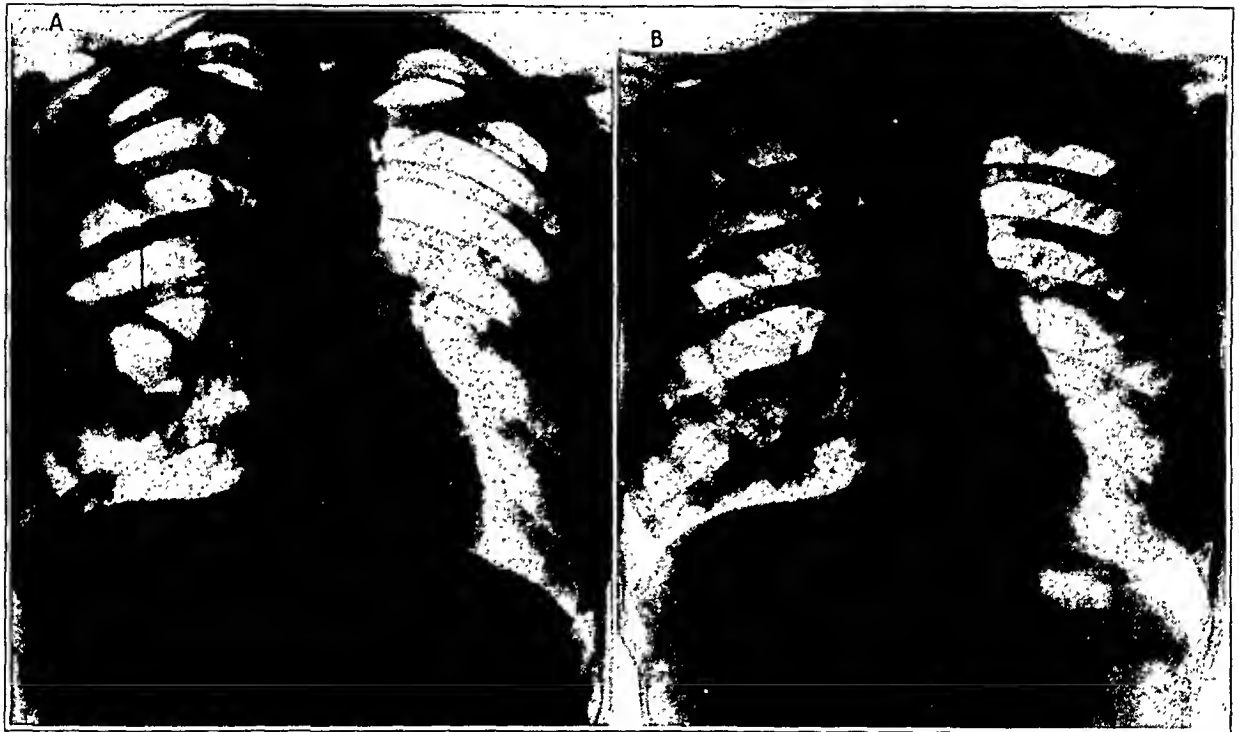


Fig. 1 (case 1).—*A*, the arrow points to a large cavity in the midst of the area of consolidation (March 15, 1926). *B*, complete disappearance of the cavity (April 15).

nomena, and who on roentgenologic examination showed a cavity in the infiltrated area in the lower lobe of the right lung, which in the course of fifteen days cleared up spontaneously. There was no clubbing of the fingers, and the sputum never had a foul odor.

CASE 2.—I am reporting the second case through the kindness of Dr. Harry Wessler. A. S., an Austrian housewife, aged 37, was first seen near the end of the pneumonic process, which involved the upper lobe and part of the lower lobe of the left lung. There was a rise in temperature for three weeks after admission to the hospital. The roentgenogram revealed a small abscess in the midst of a resolving pneumonia, the abscess being below the left clavicle. There was no expectoration at any time. On March 10, 1926, the first roentgenologic report showed a pneumonic infiltration involving the upper lobe of the left lung, and at the level of the second interspace a cavity about 2 inches in diameter, showing a

fluid level. On March 17, one week later, examination of the chest showed a marked decrease in the extent and density of the infiltration previously reported in the left lung, and the cavity was distinctly smaller. On March 26, the cavity had completely disappeared.

CASE 3.—D. C., a graduate nurse, who had had a previous attack of pneumonia in 1923, entered the hospital on Jan. 6, 1929, with a history of chill, fever, cough and pain in the chest of twenty-four hours' duration. She had all the signs and symptoms of a right lobar pneumonia, and pneumococcus type III was recovered from the sputum. Blood cultures were negative. The course of the disease was rather severe, ending by crisis on the tenth day, after which convalescence was slow but uneventful. On January 19, roentgenologic examination of the chest showed partial consolidation of the lobes on the right side. The roentgen appear-

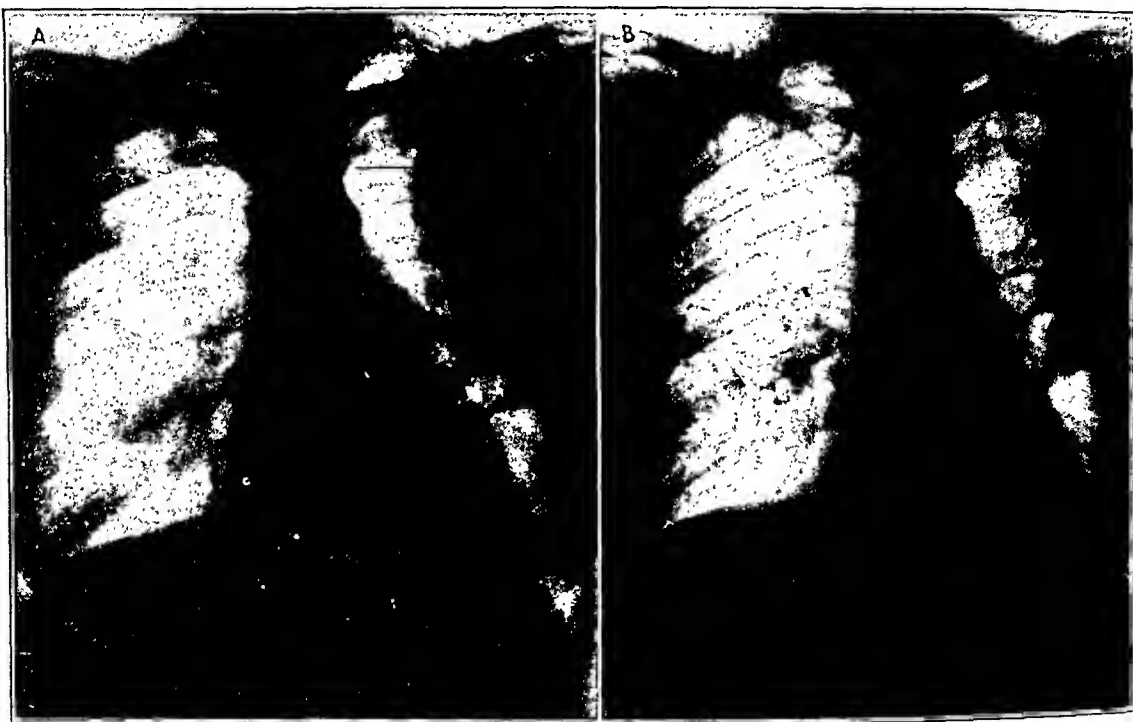


Fig. 2 (case 2).—*A*, the arrow points to the cavity (March 10, 1926). *B*, disappearance of the cavity (March 26).

ance was that of a resolving pneumonic process. The left side was clear. The heart was normal in size and shape. On February 16, examination of the chest showed a faint pneumonic infiltration occupying the right infraclavicular region from the level of the first to the third ribs anteriorly. Within this infiltrated area there was a small cavity, $\frac{1}{2}$ inch (1.27 cm.) in diameter. The patient was again examined roentgenologically on her return from the country on April 2, and examination of the chest showed resorption of the infiltration previously reported in the upper lobe of the right lung, and the cavity previously noted had entirely disappeared. At no time did she have symptoms referable to the cavity, and there was no cough, expectoration, foul breath or clubbing of the fingers.

CASE 4.—V. E., a Spanish housewife, aged 22, entered the hospital twelve days after the onset of bronchopneumonia, with a history of dyspnea, weakness, chilliness and fever. The physical signs were those of resolving bronchopneumonia.

On admission to the hospital the temperature was 102.8 F.; it came down to normal three days after entrance, and remained there. The white cell count was 12,100, with 77 per cent polymorphonuclears. A roentgenogram of the chest, taken on April 17, 1928, showed a pneumonic infiltration at the base of the left lung, with a cavity within it about $1\frac{1}{2}$ inches (3.77 cm.) in diameter. The roentgen appearance was that of an abscess of the lung. There was no cough, expectoration, foul sputum or a foul odor to the breath. The roentgenogram taken on May 3 showed a marked decrease in the pneumonic infiltration previously noted in the lower lobe of the left lung. The cavity was faintly indicated and was somewhat smaller. Three days later, the patient was discharged, symptom-free and having gained 9 pounds (4.1 Kg.).

CASE 5.—M. U., a Polish housewife, aged 40, was admitted to the hospital with a history of severe chill, hemoptysis and pain in the left axilla for two weeks

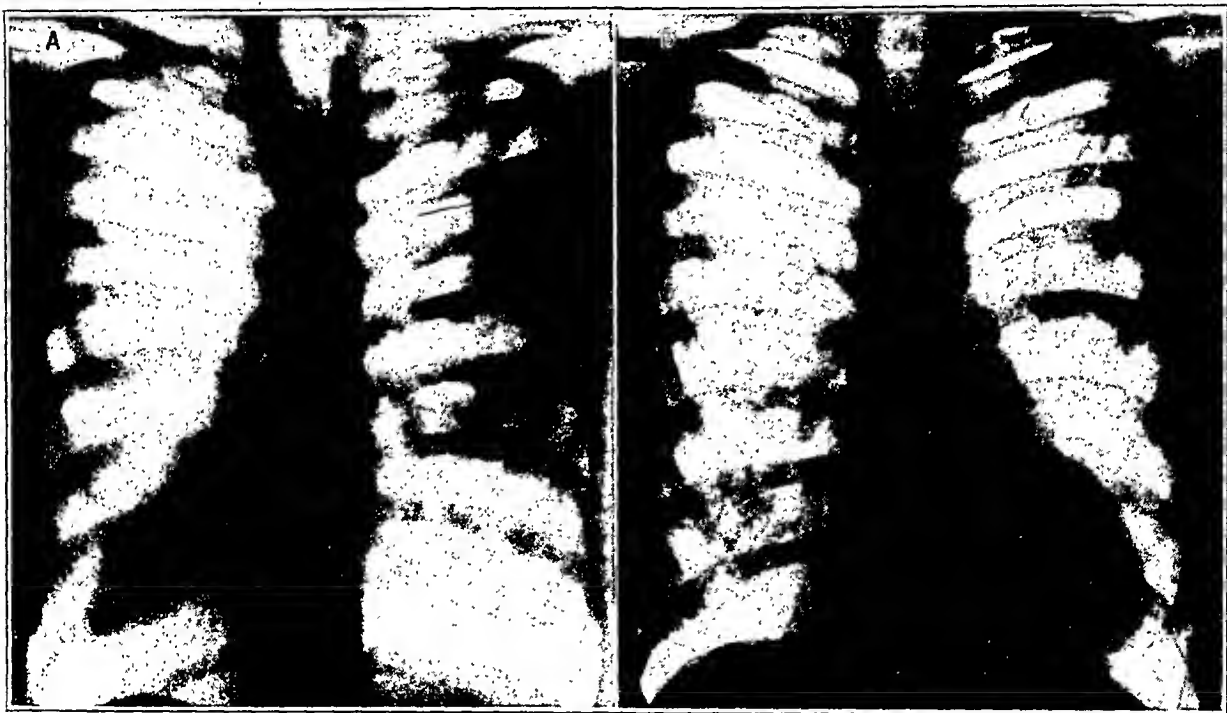


Fig. 3 (case 3).—*A*, the arrow points to a small area of cavitation in the midst of the area of pneumonic consolidation (Feb. 16, 1929). *B*, the cavity has completely disappeared (April 2).

before admission. The fever lasted for one week, and herpes labialis was present. She remained afebrile for five days, and then two days before admission there was another rise in temperature, and she suffered from a paroxysmal non-productive cough. Physical examination revealed dullness, diminished breathing and numerous râles at the base of the left lung and left axilla. She was regarded as having resolving pneumonia, but the roentgenogram taken as a routine measure showed the presence of a diffuse infiltration at the lower lobe of the left lung, in the center of which was a cavity with a fluid level. On the basis of these observations, the diagnosis of a postpneumonic abscess of the lung was made. The roentgenologic history of the case was as follows: Jan. 30, 1929: "Examination of the chest showed a collection of fluid at the left base, which showed a horizontal level at the eighth rib posteriorly. This fluid was walled off above. The roentgen examination was more suggestive of a localized collection of fluid and air in the

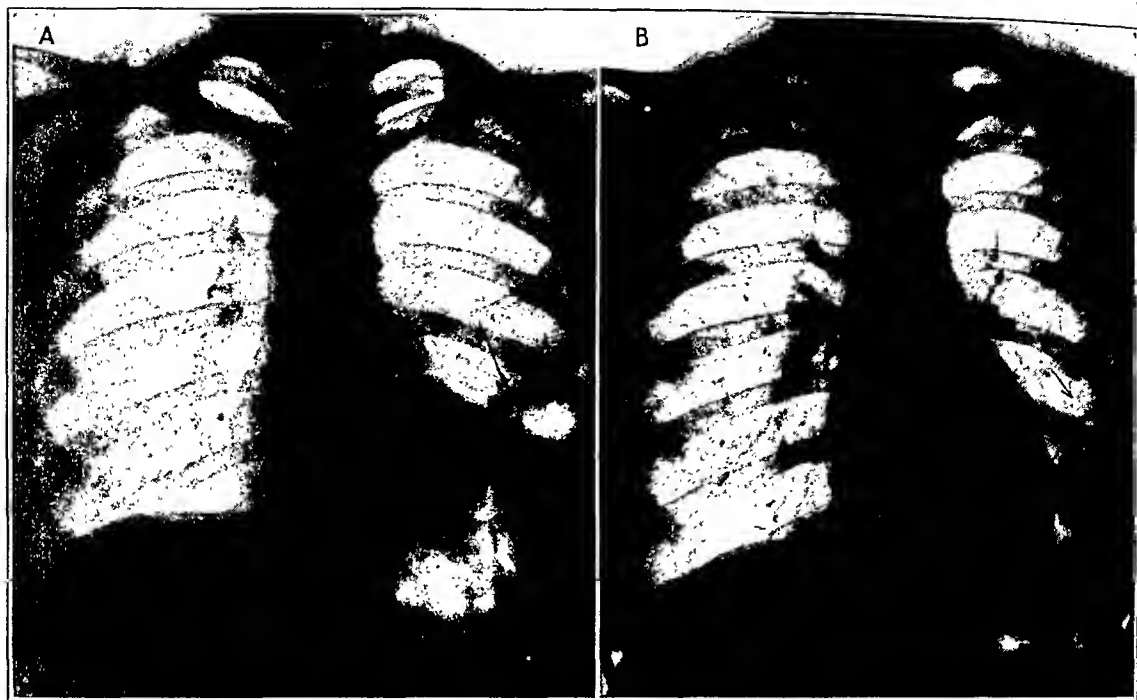


Fig. 4 (case 4).—*A*, the arrow points to a cavity in lower lobe of the left lung (April 17, 1928). *B*, diminution in the size of the cavity (May 3).



Fig. 5 (case 5).—*A*, the arrow points to a cavity, showing fluid level (Jan. 30, 1929). *B*, the cavity has disappeared (March 1).

pleura than of an abscess of the lung. However, a definite differential diagnosis could not be made." February 5: "Examination of the chest, in comparison with the films of January 30, showed a fairly marked diminution of the consolidation in the region of the left lower lobe. The cavity, however, was still visualized. It showed a fluid level and measured about $1\frac{1}{2}$ inches in diameter." February 11: "Roentgen examination of the chest showed a further decrease in the size of the cavity previously noted in the left lower lobe. From the roentgen and clinical examinations, it was suggested that this might be a case of simple necrosis of the lung following pneumonia." February 20: "Examination of the chest showed a further decrease in the infiltration in the left lung. The cavity which was previously noted had almost disappeared." March 1: "Examination of the chest

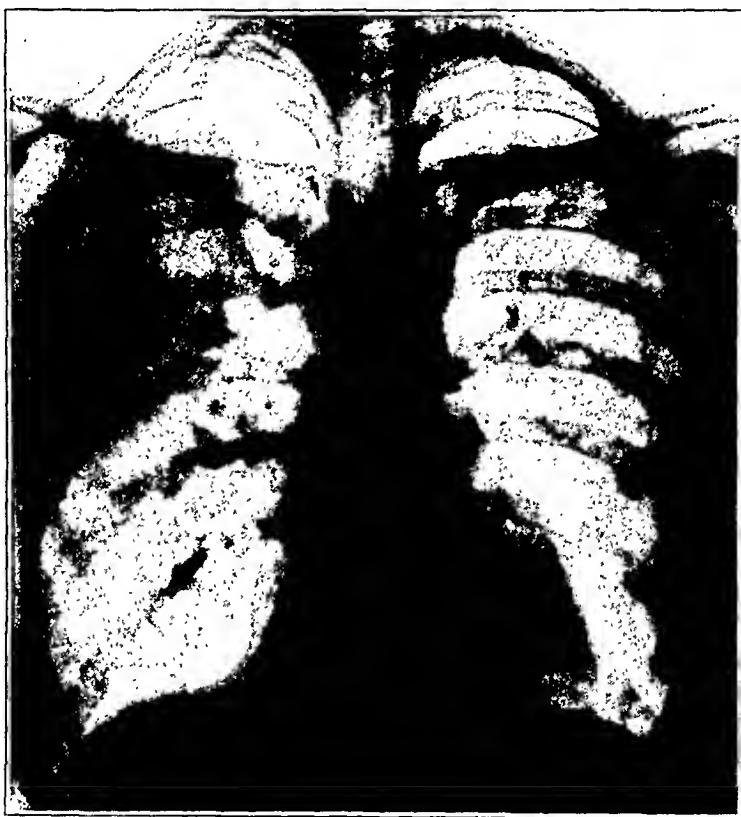


Fig. 6 (case 8).—Roentgenogram, showing area of pneumonia (March 19, 1929). No cavity is visible. No subsequent plates were taken. The area of necrosis was discovered at autopsy.

showed a decrease in the area of infiltration previously reported in the left lung. The cavity had completely disappeared." May 15 (follow-up): "Examination of the chest showed almost complete disappearance of the infiltrations previously reported in the left lower lobe. The cavity was no longer seen." The patient did extremely well clinically, remaining afebrile, gaining weight and having little or no cough. Again there was no foul sputum, clubbing of the fingers or profuse expectoration.

Three patients have been seen by me in whom there was no clinical evidence of an area of pulmonary necrosis, nor was roentgenologic evidence obtained, mainly because the patients were too ill to have

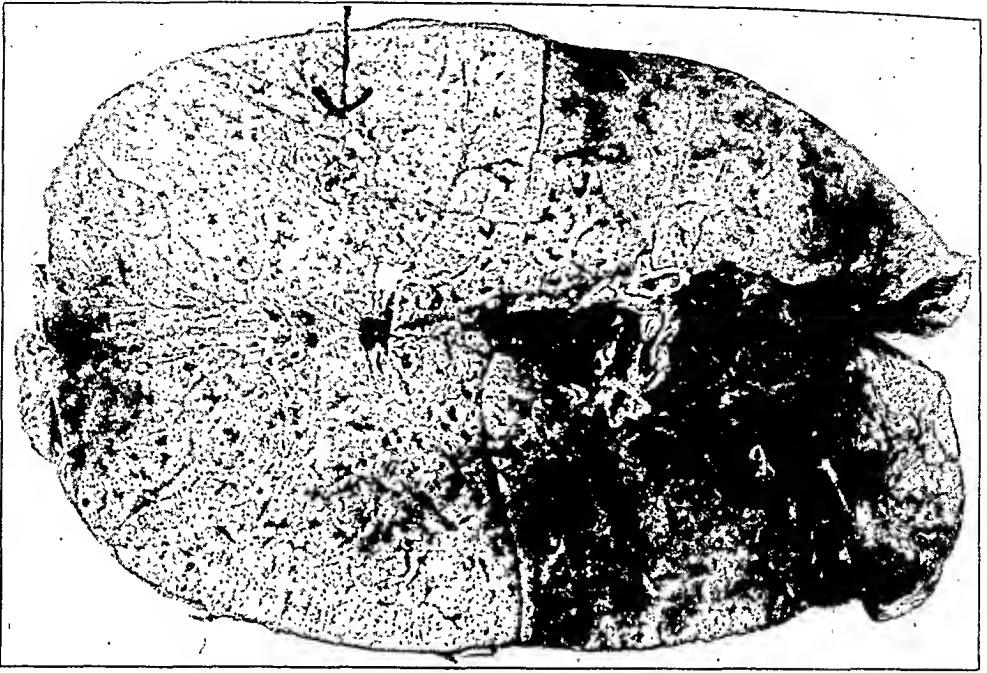


Fig. 7 (case 8).—Gross section. The arrow points to the area of aputrid necrosis.

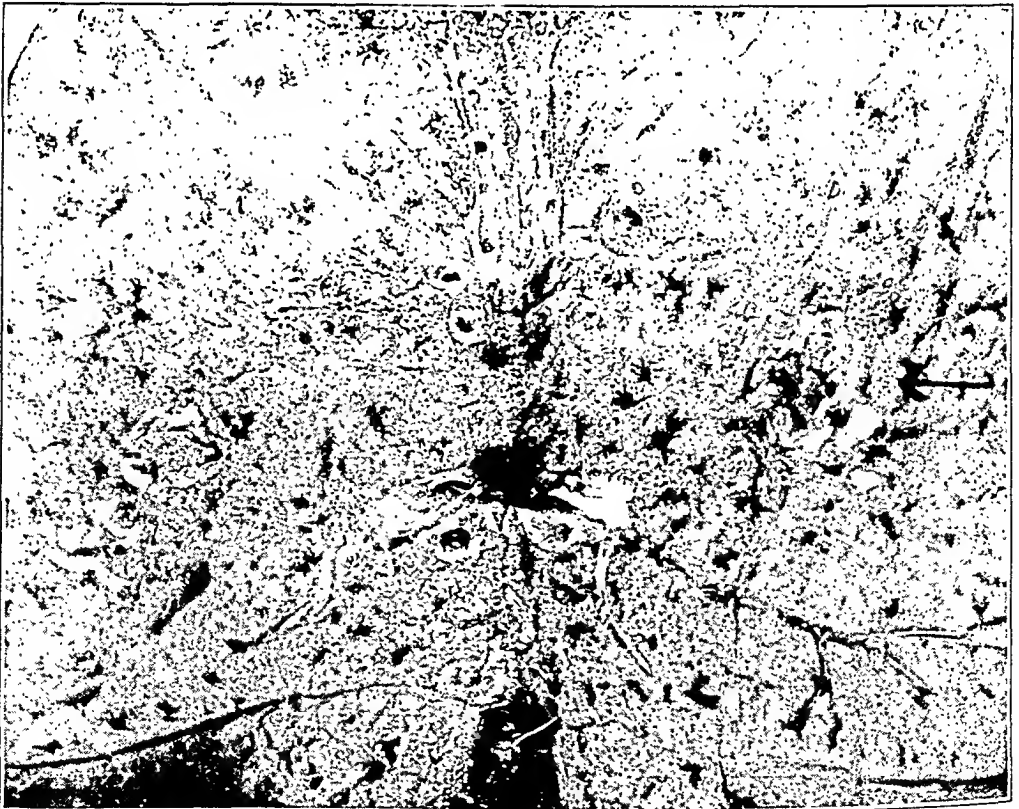


Fig. 8 (case 8).—Gross section. The arrow points to the area of aputrid necrosis.

repeated roentgenograms taken. These patients (cases 6, 7 and 8) died and came to autopsy.

CASE 6.—I. S., a Greek peddler, aged 38, entered the hospital five days after the onset of illness, showing signs of pneumonia of the upper and middle lobes of the right lung. The course of the disease was severe and the patient died on the eighth day after admission. Autopsy disclosed a lobar pneumonia of the upper and middle lobes of the right lung. The lung appeared grayish red and granular and contained a number of small loculated cavities containing yellowish material. Microscopic examination showed thrombosis of the arteries to the region of a caseating cavity.



Fig 9 (case 8).—Thrombosed artery outside the wall (infiltrations).

CASE 7.—M. W., a Russian, aged 64, entered the hospital desperately ill with pneumonia of the upper lobe of the left lung and myocardial insufficiency; he died within thirty-six hours of admission. Postmortem smear and culture of the lung showed pneumococcus type II. The upper lobe of the left lung was in gray hepatization. In the lower part of the lobe, there was a sharply delimited area of necrotic lung tissue that had no foul odor. The area measured about 5 cm. in diameter.

CASE 8.—E. K., a Hungarian housewife, aged 34, entered the hospital on March 17, 1929, on the second day of an acute illness, with pain in the right side of the chest and the physical signs of pneumonia of the upper lobe of the right lung. She had a type II pneumococcus in the blood. The white cell count was 22,900,

with 90 per cent polymorphonuclears. The course of the disease was extremely stormy, and in spite of cardiac stimulation and the use of the oxygen tent, the patient died on the ninth day after admission to the hospital. An abstract of the important features of the autopsy was supplied by Dr. Rabin and read as follows: "Lobar pneumonia, right upper and middle lobes in gray hepatization. Lobar pneumonia, right lower lobe, in red hepatization. In the middle of the right upper lobe are two areas of necrotic lung tissue rather sharply demarcated from the surrounding lung. No bronchial communication can be made out. The cavity does not fill on injection of the bronchial tree with NaI. The bronchi show no change and contain no secretion. Microscopic examination shows the involved area to consist of a cavity filled with polynuclear cells. The wall shows necrotic lung tissue, but no increase in infiltration over the surrounding consolidated lung—thus differing from the ordinary abscess cavity. In the wall are a number of thrombosed blood vessels. Outside the cavity there is an artery whose wall is infiltrated, and whose lumen contains a thrombus."

COMMENT

From a study of the cases that I have described clinically and an examination of the roentgenograms, and from the evidence supplied by the autopsy reports, it appears that in the course of lobar pneumonia areas of apurrid necrosis may occur within the infiltrated area. These areas of pulmonary necrosis produce neither symptoms nor signs. There is no clubbing of the fingers or increased cough, and the sputum does not become foul. The condition is not suspected clinically, and is brought to light, if at all, by a roentgenogram of the chest taken as a routine measure. From what I have learned, it would seem that the sequence of events is as follows: Given the conditions that are as conducive to thrombotic phenomena as those present in the stage of hepatization in lobar pneumonia, there probably occurs a thrombosis of a vessel leading to a portion of the involved lung; the occurrence of this thrombosis is favored by any one or more of the following phenomena: (1) the pulmonary compression exercised by the pulmonary exudate, (2) compression of the capillary bed, (3) increased coagulability of the blood during the course of pneumonia, (4) lowering of the blood pressure and (5) myocardial failure with attendant slowing of the circulation. When thrombosis of the vessel has taken place, the portion of the pulmonary tissue supplied by this vessel becomes the site of infarction and subsequent necrosis. This area produces the picture of an abscess cavity in the roentgenograms. I have thought that the disappearance of these areas in so short a time was due to autolysis in the involved zone. The absence of cough and sputum is caused because the area of pulmonary necrosis did not communicate with the bronchus, and I have felt that the noncommunication of this area with the bronchus supplies the reason for the absence of the anaerobic infection, which occurs so commonly in connection with abscess of the lung.

I have searched the literature and have failed to find a clinical description of this condition. If a roentgenogram were taken as a routine procedure in resolving pneumonia, I feel certain that aputrid pulmonary necrosis would be disclosed with much greater frequency, and if searched for at autopsy would probably be found as a rather common occurrence. The areas are easily overlooked in a cut section of the lung at autopsy, and unless one knows that the condition does occur, it is readily missed.

SUMMARY

1. The clinical history and roentgenologic observations of five cases of aputrid pulmonary necrosis have been described.
2. The clinical course and autopsy observations in three others were described.
3. Aputrid pulmonary necrosis produces no symptoms.
4. It is either discovered as a roentgenologic observation or disclosed at autopsy.
5. It is probably not an uncommon observation if looked for.
6. Aputrid pulmonary necrosis is differentiated from abscess of the lung complicating pneumonia by the absence of increased cough, foul sputum and clubbing of the fingers and by the fact that the cavity heals spontaneously in a relatively short time.

THE INFLUENZA EPIDEMIC OF 1928

A STUDY OF ITS BACTERIOLOGY*

EUGENE F. TRAUT, M.D.

AND

RUSSELL D. HERROLD, M.D.

CHICAGO

The conflicting opinions concerning the specific cause of the epidemic of influenza in 1918 make a study of the epidemic of 1928 of added importance. In the recent epidemic, though obviously less severe than that of 1918, the condition resembled closely the milder infections of the previous epidemic. The principal reports of the bacteriologic observations of the 1918 epidemic center around: (1) the influenza bacillus, (2) *Bacterium pneumosintes* and (3) a specific streptococcus. Mathers, Tunncliffe,¹ Jordan,² Rosenow³ and others described a green-producing streptococcus growing characteristically as large, flat, moist colonies on blood agar plates. It was usually capsulated and lanceolate. It was ordinarily not dissolved by bile and did not ferment inulin. Agglutination and absorption experiments indicated a close immunologic alliance of the majority of the strains. Agglutinins, of low titer, were reported in the serum of patients. Tunncliffe demonstrated the development of specific opsonins during the course of the disease, one of the most important proofs of the relation of this streptococcus to influenza.

EXPERIMENTAL DATA

Cultures from the nasopharynx and sputums in the recent epidemic gave almost uniformly a predominating growth of green-producing streptococci. They appeared in large, moist colonies on blood agar plates. They were frequently mucoid. In two instances in which sputum of typical cases was injected into mice, one mouse died in eighteen hours, and the cultures of the heart's blood gave large mucoid colonies although the original cultures on plates of the sputum were not mucoid. From the heart's blood of the other mouse that died

* Submitted for publication, Aug. 26, 1929.

* From the John McCormick Institute for Infectious Diseases.

1. Tunncliffe, Ruth: Phagocytic Experiments in Influenza, *J. A. M. A.* **71**: 1733 (Nov. 23) 1918.

2. Jordan, E. O.: *J. Infect. Dis.* **25**:28, 1919.

3. Rosenow, E. C.: Studies in Influenza and Pneumonia: III. The Occurrence of a Pandemic Strain of *Streptococcus* During the Pandemic of Influenza, *J. A. M. A.* **72**:1608 (May 31) 1919.

in forty-eight hours, the colonies were not mucoid and were similar to the growth on the original nasopharynx or sputum plates. This would seem to indicate an increased virulence when mucoid. This mucoid character would frequently be lost after long cultivation on artificial medium. The mucoid appearance might return in subsequent transfers to moist mediums. The loss of mucoid character recalls the type 3 pneumococcus in which artificial cultivation is followed by a change to smaller colonies with little or no tenacious quality.

In almost every instance, gram-negative diplococci were present in a proportion of from 10 to 75 per cent of the typical streptococci. This combination of pebbly gray diplococcus colonies and larger green streptococcus colonies was so constant as to make the gross recognition of plates from patients with influenza extremely easy.

TABLE 1.—*Origin of Strains*

Number of Culture	Main Features of the Disease	Day of Disease Cultured	Comment
1	Fever; chills; prostration; pharyngitis	14	Cough only symptom at time of culture
2	Temperature, 101 F.; chill at onset; prostration; pharyngitis	2	
3	Slight rise in temperature, 99.6 F.; prostration	2	
4	Fever; prostration; generalized aching; nasopharyngitis	2	Culture on third day similar in all respects to first culture
5	Fever; prostration; coryza; sore throat; cough; leukopenia	3	
6	Fever; prostration; generalized aching; coryza; cough	2	
7	Fever; generalized aching; headache; weakness; cough	2	
8	Fever; chills; cough; prostration; coryza	5	
9	Fever; chills; generalized aching.....	2	
10	Chills; fever; prostration; cough (lasted four weeks after acute attack)	7	

Microscopically, the streptococci are lanceolate. They were in pairs and short chains. Growth was abundant in dextrose broth, and usually without clumping.

The serum from some of the more typical cases was tested for the presence of agglutinins for this streptococcus. The results were not conclusive. The serums from the patients recovering from the disease contained agglutinins in higher titer than did the control serums. The best results were obtained by the use of one part of serum to three parts of streptococci suspension. Uniform results could hardly be expected. The serum from patients convalescent from pneumonia gives less than 50 per cent positive agglutination results in an equally low dilution. Furthermore, some strains, particularly soon after isolation, are likely to be less agglutinable than others. The convalescent serum from patient 3 agglutinated six of the ten strains. That from patient 6 agglutinated five of ten strains, including the same strains agglutinated by the serum of patient 3.

Virulence tests were made on mice. Sputums 9 and 10 were pathogenic for mice. The flora from cases 1 and 7 and 8 inclusive were not tested for virulence until some time after isolation. Only one strain was virulent at this time. The injection of the filtrate of the broth cultures of virulent strains simultaneously with the suspensions of the avirulent strains did not appear to enhance the virulence of the avirulent streptococci (table 2).

The strains were tested for fermentative ability. The results with nine of the ten strains indicated a close relationship in their common inability to ferment salicin and mannite. All ten strains fermented dextrose, saccharose and maltose. Eight fermented raffinose; eight lactose, and only four inulin. The fermentation of inulin is rather an

TABLE 2.—*Virulence Tests. Attempts to Enhance the Virulence by Simultaneously Injecting Filtrates from Virulent Cultures*

Mouse	Material Injected Intraperitoneally	Result	Postmortem Culture
1	1 cc. filtrate of 8M.....	Chill; recovery	
2	1 cc. filtrate of 9M.....	Chill; death in 15 hours	Heart's blood B. coli Peritoneal fluid B. coli
3	0.5 cc. suspension of 6.....	Death 15 hours	Heart's blood } Streptococcus Peritoneal fluid } recovered
4	0.5 cc. filtrate of 8M; 0.5 cc. suspension of 6	Death 15 hours	Heart's blood } Streptococcus Peritoneal fluid } recovered
5	0.5 cc. suspension of 4.....	Recovery	
6	0.5 cc. filtrate of 8M; 0.5 cc. suspension of 4	Recovery	
7	0.5 cc. suspension of 2.....	Recovery	
8	0.5 cc. filtrate of 9M; 0.5 cc. suspension of 2	Recovery	
9	0.5 cc. suspension of 5.....	Recovery	
10	0.5 cc. filtrate of 9M; 0.5 cc. suspension of 5	Recovery	

inconstant observation in standard, well studied strains of streptococci and even pneumococci. The three strains pathogenic for mice had similar sugar reactions. After passage through mice their sugar fermentations did not change.

Only one of the three atypical strains in the fermentation experiments fermented salicin. One of these (strain 1), was isolated two weeks after the onset of the disease. Although the patient had persistent cough, he had no fever or other symptoms of acute influenza. It is possible that the specific streptococcus had disappeared. This strain fermented inulin. Strains 4, 5, 6, 7, 8 and 9 were typical types and were isolated early in the course of the disease.

The major difference between our fermentations and those of Tunnicliff was the almost complete absence of salicin fermentation in our series. Our tests were made after a shorter period of growth on artificial mediums. Possibly her strains acquired this ability on prolonged artificial cultivation (table 3).

Four of the ten strains were dissolved by 10 per cent bile. None of them was dissolved by 5 per cent bile. Fifty per cent bile dissolved all of them. We employed twenty-four hour cultures in dextrose-broth as advised by Kelly and Gussin.⁴ All except no. 6 of the bile-soluble cultures fermented inulin. One (no. 2) of the cultures that were insoluble in bile fermented inulin.

Reactions with high dilutions of the toxin in the skin of susceptible persons were not expected. *Streptococcus viridans* and *Pneumococcus* seldom produce toxins giving reactions of 2 cm. in diameter if used in dilutions greater than 1:10. The Berkefeld filtrates of our streptococci grown five days in phosphate broth gave similar skin reactions in dilution of 1:25 in physiologic solution of sodium chloride. They were larger and occurred more frequently in persons known not to have had influenza in the recent epidemic than in the convalescent patients. Possibly those with negative skin reactions were immune as a result of previous abortive or unnoticed attacks of influenza. These are difficult to exclude in such a mild, widespread epidemic.

TABLE 3.—*The Effect of Ox Bile on Broth Suspensions of the Streptococci*

Cultures Dissolved by 10 per Cent Bile	Cultures Insoluble in 10 per Cent Bile
1, 6, 6M ₁ , 6M ₂ , 8, 8M ₁ , 9, 9M ₁ R	2, 2M ₁ , 4, 5, 7, 10

Some of the persons tested doubtless carried some degree of immunity from previous epidemic or interepidemic infections.

The filtrate of killed cultures was lethal for mice when given in sufficient doses. Intraperitoneal injections were always followed by a severe chill. The mouse would stiffen out, fall on its back and shake violently for from five to ten minutes. As far as our experiments went, there was no proof that the toxin enhanced the virulence of the simultaneously injected streptococci.

A culture (9M) recently isolated from the heart's blood of a mouse was inflated into the nares of guinea-pigs. The guinea-pigs showed no ill effects.

Sputums from acutely ill patients were applied on swabs to the nares of rabbits, with no results. The culture (9M) recently isolated from a mouse was rubbed into the nares of rabbits; there were no symptoms (table 4).

According to Fisher,⁵ swabbing the nares of rabbits with 50 per cent phenol so lowered the resistance that otherwise innocuous streptococci were able to produce disease. In the first rabbit, the left nostril was swabbed with phenol. No bacteria were injected. Death occurred in four days. No localized changes were found at autopsy. The changes

4. Kelly, F. B., and Gussin, H.: J. Infect. Dis. **35**:327, 1924.

5. Fisher, quoted by Laughlen: J. Infect. Dis. **44**:33, 1929.

were those of septicemia. An unidentified staphylococcus was isolated. No streptococci were recovered from the heart's blood.

After swabbing the nares of the next rabbit with 50 per cent phenol, we allowed 2 cc. of streptococcus 9M to flow slowly into the nose. The rabbit died in six days. Autopsy showed pneumonia of the lower lobe of the right lung. The streptococcus was recovered from the heart's blood and from the lung. This strain was then called 9MR.

This strain, more virulent for rabbits, was injected into the nares of other rabbits without preliminary preparation. It regularly produced fatal pneumonia, usually limited to the lower lobe of the right lung.

TABLE 4.—*Attempts to Produce Influenza in Rabbits*

Number of Rabbits Used	Basal Culture Before Inoculation	Material Inoculated	Treatment Before Inoculation	Symptoms After Inoculation	Basal Culture After Inoculation	Termination	Observations at Autopsy	Post-mortem Culture
2	No streptococci	Swabs with 24 hour broth suspension; 9M	None	None	No streptococci	No ill effects		
2	No streptococci	Sputum from "flu" cases	None	None	No streptococci	No ill effects		
1	No streptococci	No culture	Phenol, 50% in left nostril	Moderate purulent discharge	No streptococci	Death 4 days after phenol	No local changes; septicemia	No streptococci recovered
2	No streptococci	2 cc. broth culture, 9M	Nostril swabbed; phenol 50%	Purulent discharge; sneezing	No streptococci	Death 6 days after phenol	Pneumonia of right lower lobe	Original streptococci recovered from lung and heart's blood
1	No streptococci	9MR	Without phenol	Purulent discharge; sneezing	No streptococci	Death 6 days after phenol	Pneumonia of right lower lobe	Original streptococci recovered from lung and heart's blood

Previous injection of nonlethal doses of the streptococci or of their filtrates protected mice wholly or partly in two of the three attempts (table 5).

In the first acute flare of the epidemic, we attempted to immunize noninfected persons by vaccines made from the early isolated strains. Fifteen people were given five injections each of plate washings killed with phenol and heat, 10 cc. of a salt solution being used for the growth on each blood-agar plate. The doses were approximately 0.5, 1, 1, 1, and 1cc. The subjects were persons living in close contact with patients acutely ill with influenza. One of them, who had lost much sleep in caring for her son, a patient with influenza, developed a mild acute rhinitis. The others did not develop influenza.

Several patients with acute influenza were given from three to five smaller doses of the plate washings. This procedure seemed to shorten

the course and to ameliorate the symptoms when employed early in the disease. The difficulty of evaluating such results is apparent without a large series and the necessary controls.

With the use of suspensions of these streptococci as antigens, cross-agglutination was attempted (table 6). Intravenous injections of killed dextrose-broth cultures were made into the rabbits in graduated

TABLE 5.—*The Effects of Previous Inoculations on the Susceptibility of Mice*

Material Injected, Feb. 4, 1929	Previous Inoculations	Results	Postmortem Culture	
			Heart's Blood	Peritoneal Fluid
9, 1 cc. of broth culture	Death 1 day	Culture recovered	Culture recovered
9, 1 cc. of broth culture	1/21/29 { filtrate 9M, 0.5 cc. culture 2, 0.5 cc. 1/29/29 culture 2, 1.0 cc.	Death 1 day	Culture recovered	Culture recovered
8, 1 cc. of broth culture	Death 3 days	Culture recovered	Culture recovered
8, 1 cc. of broth culture	1/21/29 { filtrate 8M, 0.5 cc. culture 4, 0.5 cc. 2/1/29 culture 2, 1.0 cc.	Recovered		
6, 1 cc. of broth culture	Death 4 days	Culture recovered	Culture recovered
6, 1 cc. of broth culture	1/21/29, filtrate 8M, 1.0 cc.	Death 9 days	Atypical colonies original 6 (?)	Sterile

TABLE 6.—*Fermentations of Sugars and the Effect on Litmus Milk of the Streptococci*

Culture by Number	Dextrose	Saccharose	Levulose	Maltose	Salicin	Lactose	Mannite	Raffinose	Inulin	Litmus Milk	
										Acidified	Coagulated
1	+	+	+	+	+	+	0	+	+	+	0
2	+	+	+	+	0	+	0	+	+	+	+
2B	+	+	..	+	0	+	0	+	0	+	+
3	+	+	..	+	0	0	0	0	0	+	0
4	+	+	..	+	0	+	0	0	0	+	0
5	+	+	..	+	0	0	0	0	0	+	+
6	+	+	..	+	0	+	0	+	0	+	+
7	+	+	..	+	0	+	0	0	0	+	+
8	+	+	..	+	0	+	0	+	+	+	+
8M	+	+	..	+	0	+	0	+	+	+	+
9	+	+	+	+	0	0	0	+	+	+	+
9M	+	+	+	+	0	0	0	+	+	+	+
10	+	+	..	+	0	+	0	+	0	+	0
10B	+	+	..	+	0	+	0	+	..	+	..
Pneumococcus	+	+	+	+	0	0	0	+	+	+	+

doses. Finally, injections of large doses of the living broth cultures were made. The rabbits lost weight but were not otherwise ill during the period when injections were made. The rabbits were tested for iso-agglutinins at nine day intervals. After a titer of 1:80 or higher was secured, cross-agglutination was attempted. One of our rabbits died during the immunization. There were no changes in the organs except those of septicemia. The original culture was recovered from the heart's blood. Another rabbit developed an ascending paralysis and was killed. The brain and spinal cord showed no gross changes.

A gram-negative diplococcus nonpathogenic for mice or rabbits was recovered.

Numbers 1, 5 and 8 showed the most variations in the cross-agglutinations. The serum from the rabbit immunized to no. 8 agglutinated the homologous streptococci in a dilution of 1:320 but frequently failed to agglutinate the other strains. Strains 4, 7 and 10 were alike by the five antisera and apparently contained the more generalized agglutinins, but 2, 6 and 9 are closely allied. Strains 5

TABLE 7.—Cross-Agglutination by Rabbit Antisera *

Strains	Serum 2	Serum 6	Serum 8	Serum 9	Serum 10
1.....	o	c	o	o	c
2.....	c	c	c	c	c
4.....	c	c	c	c	c
5.....	o	c	o	c	c
6.....	o	c	c	c	c
6M.....	p	c	c	c	c
6M ₂	p	c	..	c	c
7.....	c	c	c	c	c
8.....	p	o	p	o	c
8M.....	o	c	..	c	c
9.....	p	p	o	c	c
9M.....	c	p	..	c	c
9MR.....	o	o	o	o	o
10.....	c	c	c	c	c
Pneumococcus.....	o	o	o	o	o
Streptococcus from sinus infection.....	o	o	o	o	p

* In this table, o indicates no agglutination or not higher than 1:10 dilution; p, agglutination, positive 1:80; negative 1:320; c, agglutination 1:320.

TABLE 8.—Attempts at Protection with Immune Serum

Culture	Antisera	Incubation	Result
6M, 0.5 cc. of plate washings.....	6, 0.5 cc.	None	Death in 12 hours
6M, 0.5 cc. of plate washings.....	2, 0.5 cc.	None	Death in 12 hours
6M, 0.5 cc. of plate washings.....	None	30 minutes	Death in 17 hours
6M, 0.5 cc. of plate washings.....	2, 0.5 cc.	30 minutes	Death in 12 hours
6M, 0.5 cc. of plate washings.....	6, 0.5 cc.	30 minutes	Recovery
6, 0.5 cc. of broth culture.....	None	30 minutes	Recovery
6, 0.5 cc. of broth culture.....	2, 0.5 cc.	30 minutes	Recovery
6, 0.5 cc. of broth culture.....	6, 0.5 cc.	30 minutes	Recovery

and 8 would seem to be a subgroup that would require further cross agglutination tests to determine the exact relationship. The less agglutinable strain 1 was not perhaps a true type, and it is significant that it was the only strain taken during convalescence. The pneumococcus tested apparently was not related to any of these strains serologically, nor was there any definite relation to the strain from the sinus infection.

The serum from the immunized rabbits was used in brief protection experiments. The serum from the rabbit immunized to streptococcus no. 6 gave complete protection to the mouse injected with a lethal dose of a homologous culture. The serum from the rabbit immunized to streptococcus no. 2 gave no protection against the culture of no. 6.

The gram-negative diplococci from patients 2 and 6 produced homologous antiserums agglutinating in 1:100 dilution. The serum from the rabbit immunized to diplococcus no. 6 failed to agglutinate diplococcus no. 2. The serum from the rabbit immunized to diplococcus no. 2 would not agglutinate diplococcus no. 6. Both antiserums failed to agglutinate any of the other strains of gram-negative diplococci, even in concentrations of 1:10.

The gram-negative diplococci found in constant association with the streptococci were avirulent for mice and rabbits. They grew abundantly on blood-agar and in broth. The blood of rabbits immunized against these diplococci as antigens failed to agglutinate the other strains of diplococci.

Ferrán⁶ isolated a gram-positive coccus from the tissues of patients fatally ill with influenza. These cocci were very virulent. The serum of patients convalescent from influenza agglutinated these cocci. He attributed protective powers to the vaccine made from this coccus.

We have never been able to identify "*Bacterium neumosintes*" in any of our cultures.

We looked particularly for Pfeiffer's bacillus but were able to identify it in only one of our cultures.

COMMENT

As the result of the careful work in the previous epidemic (1918) and the bacteriology of the respiratory secretions of the last epidemic Mather's coccus should be tentatively considered the specific cause of influenza until proof is produced to the contrary. It would seem justifiable to attempt immunization with the filtrates of this streptococcus.

SUMMARY

The flora in the sputums of patients acutely ill with influenza were identical in containing two predominating types of bacteria: green-producing streptococci and gram-negative diplococci.

The streptococci of these patients were pathogenic for animals.

These streptococci produced a toxin. Skin tests with this toxin suggested a means of determining susceptible persons.

Vaccines made from these streptococci seemed to have the power of immunizing against the influenza infection.

The green-producing streptococci for the most part reacted similarly in fermentation tests and bile-solubility tests.

These streptococci showed relationship in cross-agglutination experiments.

6. Ferrán, J.: Siglo méd. 83:401, 1929.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

II. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ONE-HALF DROP OF COMPOUND SOLUTION OF IODINE*

WILLARD OWEN THOMPSON, M.D.

Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School

EDWARD G. THORP, M.D.

PHEBE K. THOMPSON, M.D.

AND

ARCHIBALD C. COHEN, A.B.

BOSTON

We have previously shown that during the administration of 1 drop of compound solution of iodine (about 6 mg. of iodine) daily to unselected hospital patients with exophthalmic goiter, there usually occurs as marked a reduction in basal metabolism as during the administration of much larger doses.¹ The effect of administering $\frac{1}{2}$ drop of the compound solution (about 3 mg. of iodine) daily has now been observed in twenty unselected hospital patients with the disease.

METHOD

The method was the same as that used in the hospital patients who received 6 mg. of iodine daily, except that 1 drop of a 50 per cent compound solution of iodine (roughly, 3 mg. of iodine)² was administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution.

DATA

The data of the twenty cases are summarized in tables 1 and 2. It may be seen that the average basal metabolic rate shortly after

* Submitted for publication, Aug. 26, 1929.

* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

1. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, *Arch. Int. Med.* **45**:261 (Feb.) 1930.

2. Owing to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. We previously noted that when this solution was kept in a corked bottle, some reaction took place between it and the cork, as a result of which the cork was slowly destroyed and the solution became pale.

TABLE 1.—Summary of the Consecutive Effects of Rest, the Daily Administration of One-Half Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward, in Hospital Patients with Exophthalmic Goiter

Patient	Admission			Rest			On One-Half Drop Compound Solution of Iodine Daily										On Larger Doses					Estimated Weight of Thyroid Gland at Time of Operation, Gm.				
	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	No. of Days Before Reaching Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days		Size of Dose in Drops, Daily	Total Change in Basal Metabolic Rate on All Doses, Points		
Mrs. J. P.	+88	120	58.3	+59	98	55.0	-29	1	7	+32	98	52.2	-27	12	4	0	5	+83	63	51.8	+	0	30	-21		
Mrs. A. E.	+42	127	63.7	+49	115	61.9	+7	0	10	+21	92	60.8	-25	13	1-2	11	11	+21	90	61.2	+	0	30	-28		
Mr. O. G.	+45	99	61.1	+26	92	61.0	-19	1	4	+17	76	60.9	-26	12	1-2	10	10	+5	74	61.7	+	5	30	-21		
Miss E. F.	+57	141	43.6	+41	100	44.6	-16	2	4	+36	93	41.8	-24	12	1-2	8	10	+16	92	45.7	+	1	30	-25		
Mr. A. W.	+65	110	52.7	+54	105	50.8	-11	4	7	+42	85	48.3	-18	15	7	0	7	+27	88	48.4	+	9	30	-27		
Mrs. F. W.	+49	107	53.1	+25	94	52.5	-24	2	5	+7	85	52.6	-18	10	5-6	0	5-6	+4	83	52.6	+	6	30	-21		
Mr. P. M.	+63	102	62.2	+42	87	60.5	-21	2	8	+42	117	61.2	-31	11	5-6	0	0	+40	114	60.7	+	2	30	-2		
Mrs. M. B.	+50	90	48.9	+41	87	46.9	-19	7	10	+35	79	45.3	-6	12	0	0	0	+31	83	45.5	+	4	30	-13		
Miss M. P.	+35	155	43.1	+35	135	42.8	0	0	4	+14	128	42.8	-21	13	1	16	2	+22	132	41.5	+	8	30	-10		
Miss E. M.	+50	117	42.6	+41	103	41.3	-9	2	5	+12	88	41.1	-29	11	1-2	5	5	+19	94	41.6	+	7	30	-22		
Mr. L. B.	+62	99	57.5	+64	101	54.3	-40	0	8	+24	81	51.3	-40	8	1-3	13	5	+13	79	55.3	-11	9	30	-17		
Miss J. P.	+66	132	51.3	+26	113	49.6	-40	6	8	+19	110	49.2	-7	7	0	0	0	+9	112	49.7	+	10	30	-51		
Mr. T. B.	+32	85	60.7	+25	88	61.3	-7	0	5	+52	91	59.1	+27	7	0	0	0	+26	181	59.3	-26	7	30	+1		
Mrs. B. D.	+22	102	70.5	+18	93	69.0	-4	0	6	+19	99	66.3	+1	10	0	0	0	+22	103	63.5	+	3	60	+4		
Mrs. F. R.	+61	125	60.1	+51	113	58.6	-10	1	6	+29	89	59.2	-22	9	1	6-7	6-7	+21	93	60.1	+	1	30	-30		
Mrs. M. C.	+71	112	50.2	+53	112	49.0	-18	1	5	+52	70	47.8	-1	10	0	0	0	+35	71	48.5	-17	6	30	-18		
Mrs. M. McN.	+33	103	54.6	+27	89	51.4	-6	0	7	+15	82	53.9	-12	10	2	0	3	+11	76	54.1	-4	3	30	-16		
Mr. J. B.	+48	106	51.5	+47	108	50.6	-1	0	7	+70	124	49.0	+23	12	0	0	0	+36	104	48.6	-34	7	30	-11		
Mr. E. K.	+43	73	62.9	+29	64	60.9	-14	5	6	+12	62	63.9	-17	10	4-5	0	8-9	+13	64	61.3	+	4	30	-16		
Mrs. F. F.	+54	113	46.3	+50	66	45.1	-4	0	7	+14	69	45.7	-36	12	3	0	0	+9	68	46.4	+	5	30	-41		
Average																							+21	4.5	-5	-19
Average																							+17	4.5	-1	-25
All cases (20); all received large doses.....																										
All in which the basal metabolic rate dropped 10 points or more (13)																										

* The patient received 20 drops of compound solution of iodine by mistake on the fourth day only of the rest period.

TABLE 2.—Detailed Presentation of Basal Metabolism Data Summarized in Table 1*

Laboratory No.	Patient	Days Before Starting Iodine											Days After Starting Iodine																				
		11	10	9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
5767	Mrs. J. P.	A	+88	+65	+65	+65	+61	+57	+60	+47	+46	+43	+35	+32	+32	+30	+30	+34	+33†	+37	+38	S+36
5781	Mrs. A. E.	+42	+55	+47	+63	+51	+50	+47	+43	+37	+42	+31	+31	+33	+26	+26	+23	+20	+22†	+20	+22	S	
5817	Mr. C. G.	A	+45	+26	+20	+32	+20	+12	+12	+13	+9	+10	+3	-3	+1†	+0	+10	+5	S	
5833	Miss E. F.	A	+57	+45	+35	+49	+38	+30	+22	+26	+25	+21	+21	+17	+16	+18	+13†	+22	+18	+15	S+16	
5850	Mr. A. W.	A	+65	+69	+63	+55	+49	+59	+55	+44	+51	+47	+48	+38	+43	+36	+39	+35	+34	+30	+33†	+42	+25	+23 S	
5933	Mrs. E. W.	A	+49	+49	+28	+24	+25	+33	+26	+20	+3	+11	+6	+11	+5†	+7	+1	+8	+3	-1	S	
5944	Mr. P. M.	A	+63	+51	+39	+34	+53	+35	+46	+38	+32	+41	+44	+29	+47	+42	+48	+45	+18†	+43	+38	+39	S	
5957†	Mrs. M. B.	+90	+72	+57	+55	+48	+56	+42	+42	+40	+35	+32	+38	+41	+29	+37	+32	+38	+34	+27	+30	-†	+32	+20	+24	+23	S	
5995	Miss M. P.	A	+35	+34	+36	+36	+20	+14	+13	+11	+13	+11	+15	+14	+14	+22	+13†	+19	+23	+25	RII	
6001	Miss E. M.	A	+50	+41	+39	+41	+41	+34	+26	+19	+15	+10	+10	+8	+15	+17†	+21	+17	S	
6054	Mr. L. B.	A	+62	+65	+66	+62	+44	+33	+30	+24	+26	+20	+27	-†	+30	+24	+15	+10	+10	+10
6071	Miss J. P.	+63	+37	+42	+47	+38	+23	+24	+30	+20	+22	+16	+22	+22	+17†	+15	+12	+9	S
6135	Mr. T. B.	A	+32	+27	+20	+25	+27	+33	+28	+42	+50	+54†	+45	+47	+44	+24	+23	S+27
6160	Miss B. D.	A	+22	+16	+15	+20	+22	+22	+20	+18	+19	+20	+19	+23	+19	+17†	S+22
6165	Mrs. F. R.	A	+61	+52	+45	+53	+53	+49	+39	+34	+34	+32	+34	+26	+30	+31†	+23	+20	+25	+21	+13	S+23
6248	Mrs. M. O.	A	+71	+60	+62	+62	+53	+53	+58	+62	+57	+50	+53	+51	+54†	+46	+51	+48	+45	+35	S
6261	Mrs. M. McN.	A	+33	+34	+28	+22	+29	+29	+29	+23	+19	+18	+16	+15	+14	+11	+17	-†	+6	+17	S+11
6264	Mr. J. B.	A	+48	+34	+52	+52	+56	+46	+43	+48	+41	+41	+42	+47	+52	+45	+49	+68	+72†	+64	+41	+34	+37	S+36
6266	Mr. E. K.	A	+43	+41	+45	+38	+28	+31	+43	+37	+18	+19	+18	+10	+14†	+13	+15	S+12
6299	Mrs. F. F.	A	+54	+59	+60	+61	+45	+55	+45	+39	+31	+27	+23	+19	+12	+15	+16	+13†	+11	+7	S+9

* A indicates admission to hospital (nos. 5781, 5957 and 6071 were admitted on the 15th, 12th and 13th days, respectively, before starting iodine); S, subtotal thyroidectomy; RH, right hemithyroidectomy.

† represents the time of starting larger doses (30 drops daily).

‡ This patient received 20 drops of compound solution of iodine by mistake on the 8th day only before the dose of ½ drop daily was started.

admission was plus 54 per cent, that after a period of rest it was plus 40 per cent, that during the administration of $\frac{1}{2}$ drop of compound solution of iodine daily it dropped to plus 26 per cent, and during the administration of larger doses given immediately after the small dose, to plus 21 per cent. Of the twenty cases, thirteen (65 per cent) showed a reduction of 10 or more points in basal metabolism during the administration of $\frac{1}{2}$ drop daily, five showed no change, and two a rise. Seven showed a lower level (8 to 34 points) during the administration of 30 drops daily than during the administration of $\frac{1}{2}$ drop. Four of

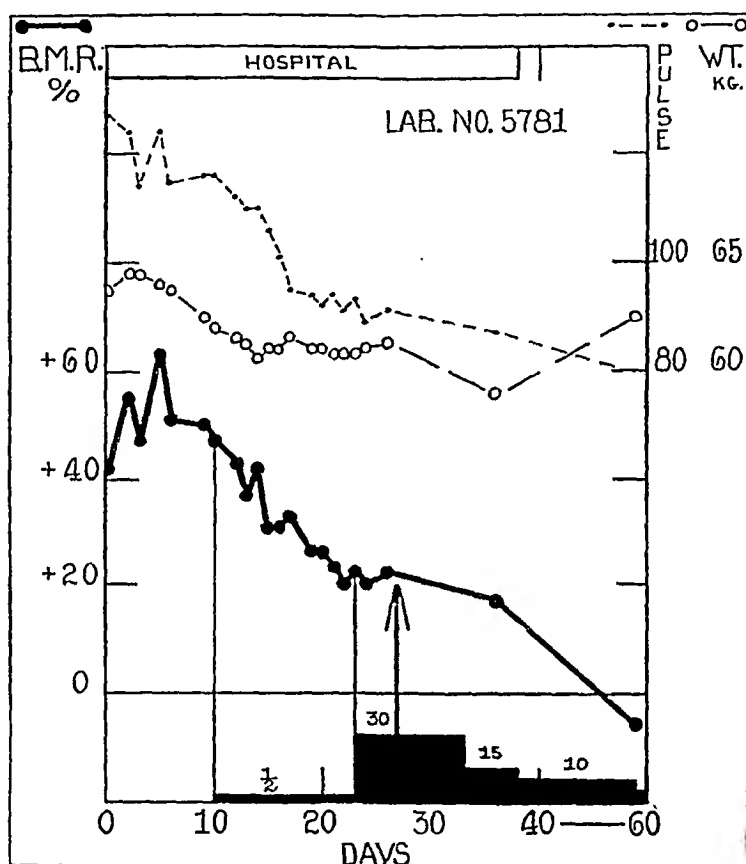


Chart 1.—Well marked reduction in basal metabolism during the daily administration of $\frac{1}{2}$ drop of compound solution of iodine, with no further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts, arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, and the figures above them, the dosage in drops.

these seven patients were among the seven who showed no reduction during the administration of $\frac{1}{2}$ drop.

Detailed data illustrating various types of response to the doses of iodine employed are recorded in charts 1 to 6.

In chart 7 the effect on basal metabolism of administering $\frac{1}{2}$ drop daily to these twenty patients is contrasted with the effect of administering 1 drop daily to the unselected house patients previously reported.¹

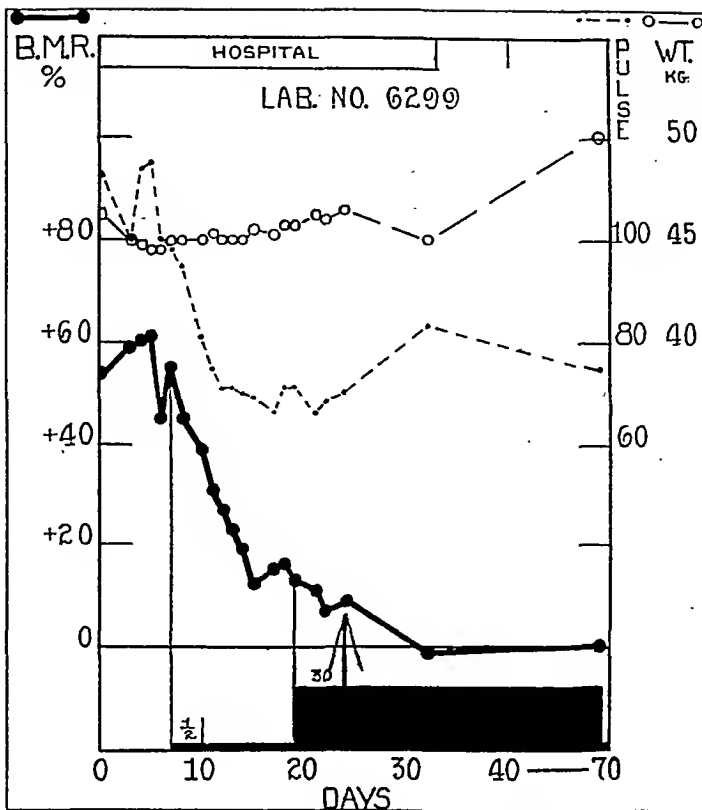


Chart 2.—Well marked reduction in basal metabolism during the daily administration of $\frac{1}{2}$ drop of compound solution of iodine, with no further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

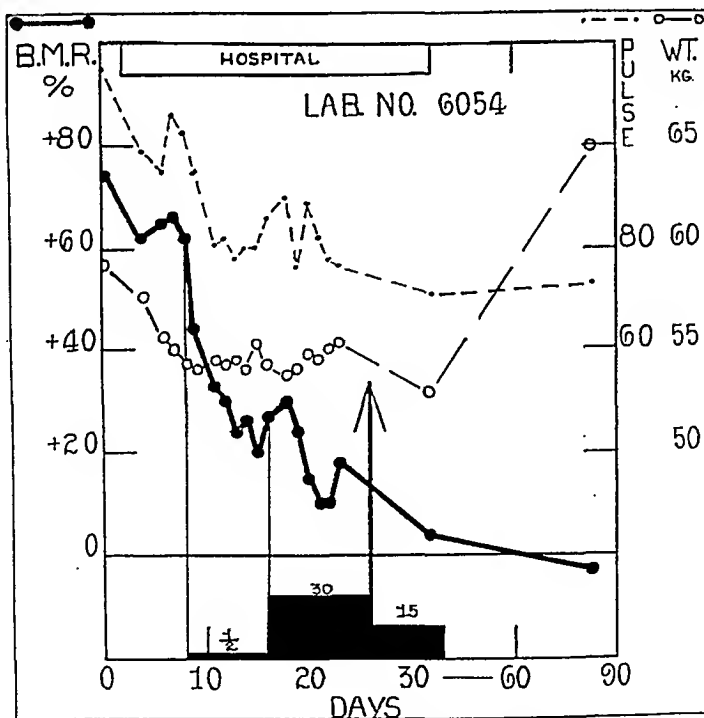


Chart 3.—Well marked reduction in basal metabolism during the daily administration of $\frac{1}{2}$ drop of compound solution of iodine and a further reduction during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

THE RATE OF DECREASE OF THE BASAL METABOLISM

In the thirteen cases which showed a significant decrease in the basal metabolism during the administration of $\frac{1}{2}$ drop daily, seven days elapsed on the average before the response became maximum. In four cases a reduction of from 8 to 18 points occurred within twenty-four hours. In three cases it was uncertain whether the drop began on the first or on the second day, and in six cases from two to seven days elapsed before any reduction was noted.

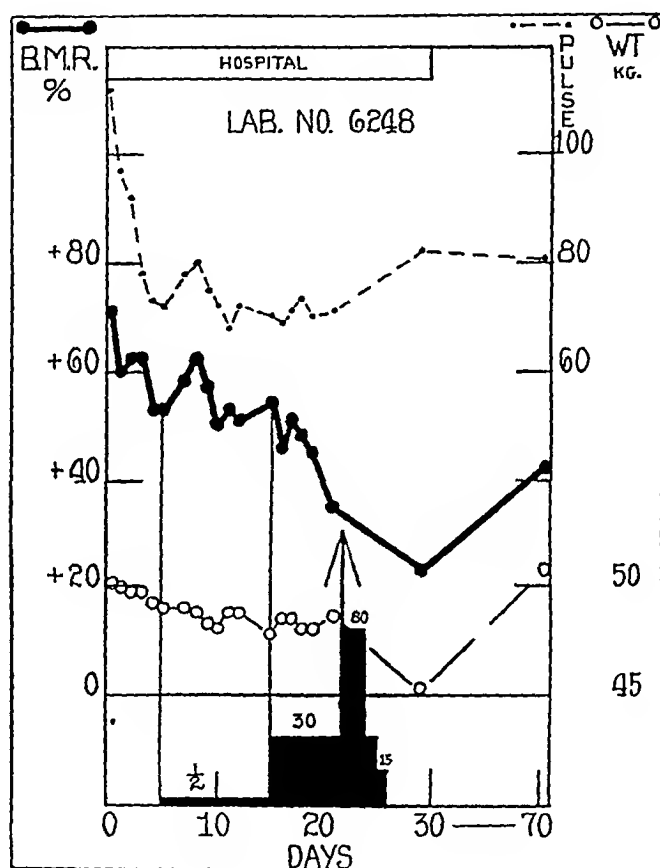


Chart 4.—No reduction in basal metabolism during the daily administration of $\frac{1}{2}$ drop of compound solution of iodine, followed by a moderate reduction in basal metabolism during the daily administration of 30 drops, preceding a subtotal thyroidectomy for exophthalmic goiter.

COMMENT

A comparison of the data with those of the 1 drop series shows two interesting differences:

1. The reduction in basal metabolism on the average was only half as great as in the 1 drop series.
2. The total response of the metabolism to all doses of iodine administered, was less.

Thus, the daily administration of 6 mg. of iodine to hospital patients¹ produced an average reduction in basal metabolism of 27 points (from plus 46 to plus 19 per cent), whereas the daily administration of 3 mg. of iodine produced an average reduction of only 14 points (from plus 40 to plus 26 per cent). This difference is less marked when only cases in each series that actually responded are considered. Thus, fifteen of the seventeen cases in the 1 drop series showed an average decrease of 31 points (from plus 50 to plus 19 per cent), whereas thirteen of the twenty cases in the $\frac{1}{2}$ drop series showed an average drop of 24 points (from plus 42 to plus 18 per cent). This difference, while

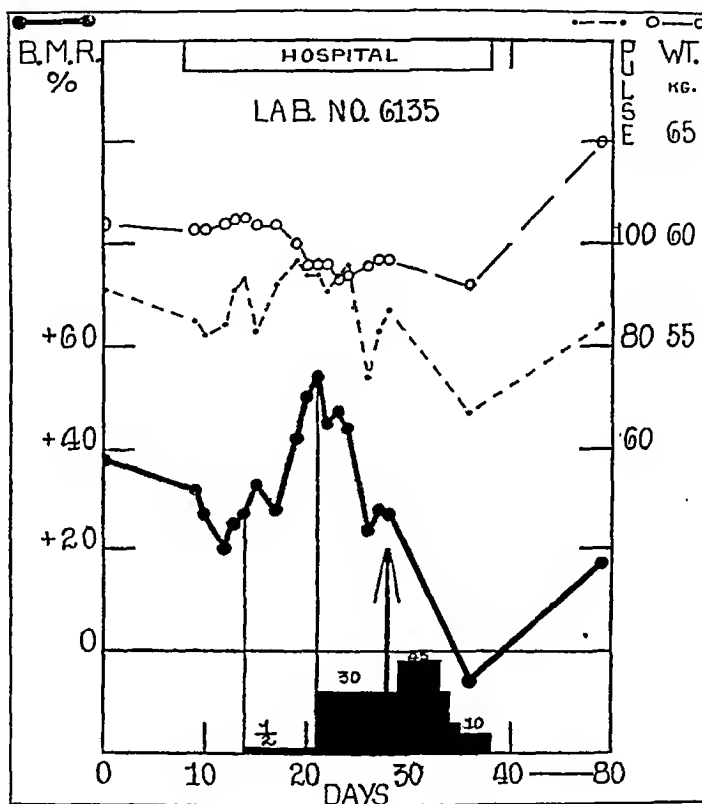


Chart 5.—A rise in basal metabolism and an increase in the severity of exophthalmic goiter during the daily administration of $\frac{1}{2}$ drop of compound solution of iodine, followed by a reduction to the pre-iodine level of basal metabolism during the daily administration of 30 drops, preceding a subtotal thyroidectomy.

in itself not great, appears more important when the results are compared with those in the $\frac{1}{4}$ drop series.³ In this connection it is of some interest that whereas the greatest decrease in basal metabolism pro-

3. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter; III. The Effect on Basal Metabolism of the Daily Administration of One-Fourth Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, *Arch. Int. Med.*, this issue, p. 430.

duced by 1 drop was 49 points, the greatest produced by $\frac{1}{2}$ drop was 40 points.

The difference between the 1 and $\frac{1}{2}$ drop series is apparent from another aspect. Thus, 88 per cent of the cases showed a significant reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, and only 65 per cent during the administration of $\frac{1}{2}$ drop daily. Therefore, in most cases of exophthalmic goiter in Boston the difference between 6 mg. and 3 mg. of iodine administered daily determines whether the effect will be marked or moderate.

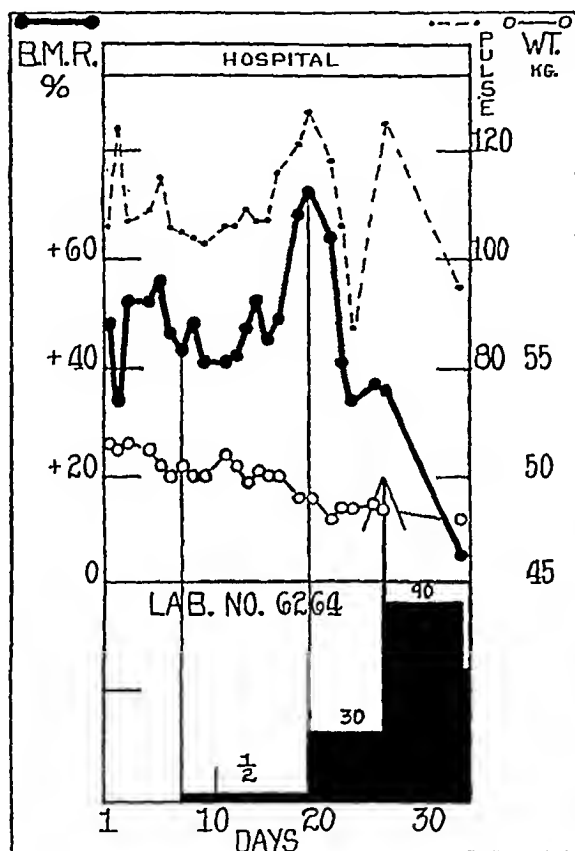


Chart 6.—A rise in the basal metabolism and an increase in the severity of exophthalmic goiter during the preoperative administration of $\frac{1}{2}$ drop of compound solution of iodine a day, followed by a reduction to a level slightly below the pre-iodine level during the administration of 30 drops a day.

Not only was the reduction in basal metabolism during the administration of $\frac{1}{2}$ drop of compound solution of iodine daily less than that during the administration of 1 drop daily, but the total response to all doses of iodine was less in the $\frac{1}{2}$ drop series. Thus, the total drop in basal metabolic rate was 19 points (from plus 40 to plus 21 per cent) on the average in the $\frac{1}{2}$ drop series, and 27 points (from plus 48 to plus 21 per cent) on the average in the 1 drop series (house patients). This difference possibly may be explained by the fact that in the $\frac{1}{2}$ drop

series large doses were administered for an average of only four and one-half days, which is probably an inadequate length of time for them to produce their maximum effect. Thus in the seven cases (5833, 5933, 6054, 6135, 6166, 6248 and 6264) in the $\frac{1}{2}$ drop series in which the effect of large doses was observed for six or seven days, the average basal metabolic rate on admission was plus 54 per cent; after a resting level was established, it was plus 44 per cent; after $\frac{1}{2}$ drop had been given daily for an average of ten days, it was plus 36 per cent; and on 30 drops a day it fell to plus 22 per cent. There is, however, the possibility that the administration of small doses may sometimes interfere with the effect of large doses administered immediately afterward—

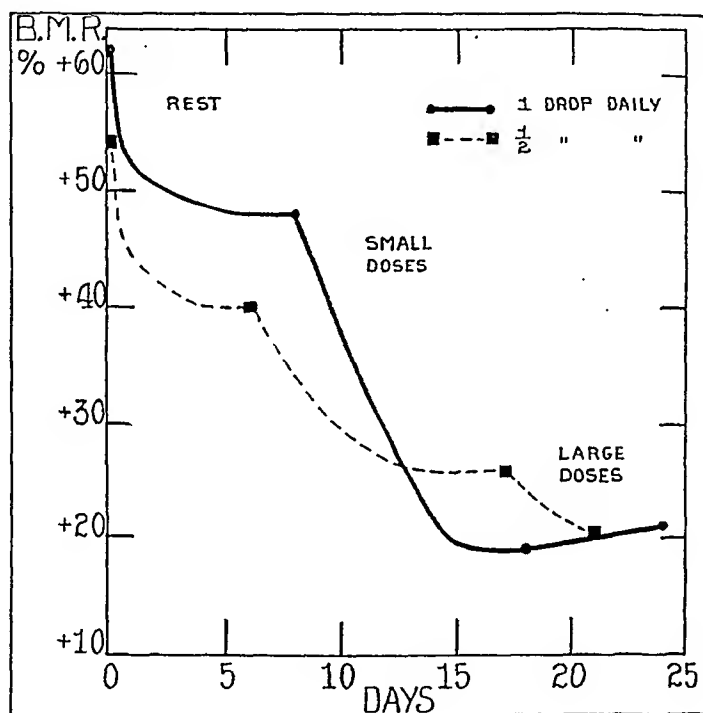


Chart 7.—A comparison of the effect on basal metabolism of the daily administration of 1 drop and $\frac{1}{2}$ drop of compound solution of iodine to two series of hospital patients. In each instance the first point recorded is the average of the basal metabolisms shortly after admission, the second point is the average resting level of metabolism, the third point is the average of the levels to which the metabolism fell during the administration of small doses ($\frac{1}{2}$ and 1 drop daily) and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually 30 drops daily). In the 1 drop series only those cases are considered in which the effect of larger doses was noted. The points in each series are arbitrarily connected by curved lines, as these denote the actual course of the basal metabolism more nearly than do straight lines.

a conclusion which appears to be upheld by the data on some of the patients in the $\frac{1}{4}$ drop series. A further comparison of the effects of these two doses will be made in the paper on the effect of administering $\frac{1}{4}$ drop daily. This paper contains a summary of our results to date.

SUMMARY AND CONCLUSIONS

During the administration of $\frac{1}{2}$ drop of compound solution of iodine (3 mg. of iodine) daily to twenty unselected hospital patients with exophthalmic goiter, thirteen showed a significant reduction in basal metabolism, five showed no change and two showed an increase. Seven showed a lower level of basal metabolism during the subsequent administration of 30 drops daily than during the administration of $\frac{1}{2}$ drop daily.

The average reduction in basal metabolism during the administration of $\frac{1}{2}$ drop of compound solution of iodine daily was 14 points (from plus 40 to plus 26 per cent)—which was only about half as great as that during the administration of 1 drop daily.

The total decrease in metabolism from all doses of iodine was less than in the 1 drop series.

In the thirteen cases that responded, the maximum reduction in basal metabolic rate appeared on the average in seven days. In four cases a reduction occurred within twenty-four hours.

The daily oral administration of 3 mg. of iodine in the form of compound solution of iodine is inadequate to produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston, whereas 6 mg. is adequate.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

III. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ONE-QUARTER DROP OF COMPOUND SOLUTION OF IODINE AND OF SLIGHTLY SMALLER DOSES, WITH A SUMMARY OF RESULTS TO DATE*

WILLARD OWEN THOMPSON, M.D.

Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School

ARCHIBALD C. COHEN, A.B.

PHEBE K. THOMPSON, M.D.

EDWARD G. THORP, M.D.

AND

ALLEN G. BRAILEY, M.D.

BOSTON

We have already shown that the daily administration of about 6 mg. of iodine in the form of 1 drop of the compound solution produces a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter,¹ but that the daily administration of about 3 mg. of iodine ($\frac{1}{2}$ drop of the compound solution) produces on the average only about half as much reduction.² As a continuation of our study of the range of effective iodine dosage in exophthalmic goiter we have now investigated the effect of the daily administration of about 1.5 mg. of iodine ($\frac{1}{4}$ drop of the compound solution) in fifteen unselected hospital patients with the disease. Some observations have also been made on the effect of administering a slightly smaller dose ($\frac{1}{8}$ drop of the compound solution) to two house patients and to sixteen outpatients. Most of the outpatients had the disease in mild form.

* Submitted for publication, Aug. 26, 1929.

* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital.

1. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, *Arch. Int. Med.* **45**:261 (Feb.) 1930.

2. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter. II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, *Arch. Int. Med.*, this issue, p. 420.

METHOD

The same routine was followed with the $\frac{1}{4}$ drop series and with the two hospital patients who received $\frac{1}{5}$ drop daily, as with the hospital patients who received 1 drop daily,¹ except that 1 drop³ of a 25 per cent compound solution of iodine (about 1.5 mg. of iodine) and 1 drop of a 20 per cent solution (about 1.2 mg. of iodine) respectively were administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution.

With the outpatients who received $\frac{1}{5}$ drop daily, the same routine was followed as with the outpatients who received 1 drop daily.

DATA

The data are summarized in tables 1, 2 and 3.

Seven of fourteen patients (50 per cent) at rest in bed showed a significant reduction in basal metabolism (10 or more points) during the administration of $\frac{1}{4}$ drop of compound solution of iodine (i. e., 1 drop of 25 per cent solution) daily; six showed no change, and one showed a rise. The average basal metabolic rate shortly after admission was plus 62 per cent; after a period of rest it was plus 43 per cent; after reaching a level on $\frac{1}{4}$ drop of compound solution of iodine daily, it was plus 34 per cent, and on larger doses administered immediately afterward it was plus 29 per cent. The corresponding figures for the seven cases that responded were plus 63, plus 42, plus 25 and plus 21 per cent, respectively (table 1). The average total drop on all doses for the whole series was only 14 points (from plus 43 to plus 29 per cent), i. e., only slightly more than on $\frac{1}{4}$ drop.

Data showing various types of response to the administration of $\frac{1}{4}$ drop daily are recorded in charts 1 to 6.

Except for the two house patients, the data on $\frac{1}{5}$ drop are not comparable to those on $\frac{1}{4}$ drop (1) because the patients were outpatients, and (2) because the majority of them had the disease in mild form.

In one of the two house patients being treated with $\frac{1}{5}$ drop daily, a reduction of 14 points in basal metabolism was noted; in the other no change occurred (chart 7). It is of interest that in neither of these was the metabolism any lower during the administration of 30 drops a day than when $\frac{1}{5}$ drop was given daily. It is also of interest that all of the outpatients who showed some reduction in basal metabolism with this dose had the disease in mild form, and in only one (no. 5272)

3. Due to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle. We previously noted that when this solution was kept in a corked bottle, some reaction took place between it and the cork, as a result of which the cork was slowly destroyed and the solution became pale.

TABLE 1.—Summary of the Consecutive Effects of Rest, the Daily Administration of One-Fourth and One-Fifth Drop of Compound Solution of Iodine and of Much Larger Doses Given Immediately Afterward in Hospital
Patients with Exophthalmic Goiter

Patient	Admission			Rest			On ¼ Drop Compound Solution of Iodine Daily										On Larger Doses												
	Laboratory Number	Age	Height, Cm.	Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	No. of Days Before Resting Level Was Reached	Length of Time Effect Was Observed, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose in Drops, Daily	Total Change in Basal Metabolic Rate on All Doses, Points	Estimated Weight of Thyroid Gland at Time of Operation, Gm.	
Mrs. M. T.	6314	41	162	+77	123	48.7	+71	110	48.6	-9	4	0	7	+61	101	50.0	-7	11	0	0	0	+61	96	49.3	-3	7	30	-10	38
Mrs. O. E.	6408	47	157	+42	97	54.9	+27	83	53.7	-15	4	0	9	+1	69	53.6	-26	9	2	0	7	+2	72	53.8	-3	5	30	-25	24
Mr. R. B.	6413	26	174	+39	72	59.2	+28	70	59.8	-11	4	1	6	+22	74	59.7	-6	10	0	0	0	+26	80	59.6	-4	4	30	-2	29
Mrs. E. S.	6423	53	166	+83	108	51.6	+27	108	50.7	-6	0	12	11	+23	104	48.9	+1	11	0	0	0	+24	103	49.0	-4	4	30	-3	29
Mrs. C. D.	6427	41	152	+84	157	44.9	+54	125	42.8	-20	7	5	10	+30	99	41.8	-24	10	0	0	0	+29	109	41.8	-2	4	30	-30	22
Mrs. A. C.	6519	53	157	+73	114	51.4	+51	93	51.3	-22	8	5	8	+37	85	49.3	-14	8	3	3	0	+29	78	51.2	-17	12	30	-31	34
Miss R. R.	6537	13	149	+92	154	38.7	+30	122	38.1	-22	1	10	10	+35	126	37.3	+5	10	0	0	4	+20	107	38.3	-7	10	30	-17	154
Mrs. A. L.	6539	46	163	+60	90	62.6	+46	83	60.5	-14	2	7	12	+36	81	57.5	-10	12	1	1	0	+31	80	56.9	-7	6	30	-1	60
Mrs. R. S.	6542	41	156	+45	108	71.2	+36	100	70.1	-9	3	4	9	+30	69	69.0	-6	12	0	0	0	+23	71	69.7	-2	7	30	-8	43
Mrs. A. B.	6558	20	151	+61	126	50.9	+28	76	46.7	-33	16	18	12	+15	80	48.7	-13	10	3	0	0	+15	95	50.0	-4	3	30	-13	29
Mrs. R. D.	6570	35	154	+53	122	50.4	+47	121	49.3	-6	0	6	12	+26	99	48.7	-21	12	3	4	0	+31	96	49.0	+5	3	30	-16	136
Mrs. M. S.	6580	34	157	+98	140	57.3	+60	115	54.1	-38	4	7	10	+68	119	52.8	+8	10	0	0	0	+44	106	53.5	-24	8	30	-10	190
Miss G. K.	6637	20	163	+87	146	59.8	+59	132	57.3	-28	2	4	12	+57	116	55.0	-2	12	0	0	0	+44	112	54.9	-13	10	30	-15	15
Mrs. C. N.	6634	30	169	+67	159	54.2	+41	122	52.7	-26	1	3	17	+30	109	50.0	-11	17	0	8	0	+24	109	51.1	-13	30	30	-17	17
All cases (14): all received large doses.....																													
Average: All cases in which the basal metabolic rate dropped 10 points or more (7)																													
			+62			+43		3	7	-19	11						-9	11			+20				-5	7		-14	
			+63			+42		5	8	-21	11						-17	11			+21				-4	6		-21	
Mrs. V. P.	5193	42	159	+64	102	60.1	+40	84	56.9	-24	6	9	9	+13	96	54.9	+3	9	0	4	4	+43	91	54.5	0	6	30	+3	..
Miss A. W.	5203	22	164	+51	98	71.5	+53	96	69.7	+2	0	3	9	+39	91	68.1	-14	9	1	-12	1	+49	89	67.7	...	7	15	-12	200
Average: All cases..... One case in which the basal metabolic rate dropped 10 points or more																													
			+58			+47		3	6	-11	0						-6	9			+42				+1	13		-5	
			+51			+53		0	3	+2	9						-14	9			+41				+2	20		-12	

TABLE 2.—Detailed Presentation of Basal Metabolism Data Summarized in Table 1

Laboratory	Days Before Starting Iodine													Days After Starting Iodine*																																
	13	12	11	10	9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25								
Patient	No.																																													
Mrs. M. T.	6344	A	+77	+76	+70	+71	+77	+72	+57	+65	+56	+68	+69	+71	+64†	+71	+64	+67	+67	+62	S+59					
Mrs. C. E.	6408	A	+42	+32	+28	+26	+29	+21	+15	+10	+18	—4	+5	+2†	+10	—1	+2	S+5				
Mr. R. B.	6413	A	+39	+30	+22	+30	+29	+28	+27	+27	+24	+24	+22	+24	+17†	+24	+28	+27	+25	S				
Mrs. E. S.	6423†	+33	+26	+40	+28	+37	+28	+25	+30	+35	+28	+26	+24	+22	+36†	+26	+25	+21	S				
Mrs. C. D.	6427	A	+84	+75	+68	+65	+56	+49	+56	+45	+43	+31	+31	+37	+28	+35	+27†	+25	+25	+23	S+37				
Mrs. A. C.	6519	A	+73	+65	+60	+51	+55	+47	+51	+47	+44	+39	+42	+35	+39†	+30	+23	+27	+27	+25	+22	+20	+20	+18	S				
Miss R. R.	6537	A	+52	+34	+36	+31	+35	+20	+44	+31	+25	+27	+20	+26	+30	+29	+30	+56	+35†	+43	+52	+43	+44	+23	+45	+36	+35	+22	RH					
Mrs. A. L.	6539	A	+60	+47	+47	+42	+43	+40	+35	+36	+35	+37	+31	+38	+44	+34†	+31	+35	+38	+52	+25	S				
Mrs. R. S.	6542	A	+15	+15	+36	+44	+37	+38	+40	+29	+31	+28	+28	+33†	+35	+26	+25	+33	+28	+30	S			
Mrs. A. B.	6553§	Sore throat	+38	+38	+34	+27	+26	+30	+31	+13	+22	+14	+14	+15	+15	+15†	+19	+11	S+20		
Mrs. R. D.	6579	A	+53	+46	+50	+48	+44	+40	+48	+50	+42	+32	+30	+33	+27	+27	+24	+27†	+30	+33	+31	+33	+28	S			
Mrs. M. S.	6586	A	+98	+70	+75	+61	+61	+62	+58	+65	+59	+72	+73	+68	+76	+69†	+76	+68	+86	+64	+42	+50	RH+39			
Miss G. K.	6627	A	+87	+58	+55	+63	+62	+63	+58	+45	+50	+54	+58†	+48	+48	+42	+51		
Mrs. C. N.	6634	A	+67	+46	+40	+42	+39	+38	+40	+37	+38	+37	+32	+30	+25	+31	+35	+34	+20	+31†	+35	+28	+23	+27	+26	..	+23	+22S	
Mrs. V. P.	5192	A	+61	+65	+50	+42	+34	+43	+42	+39	+44	+45†	+50	+38	S+42
Miss A. W.	5203#	A	+51	+53	+54	+53	+41	+44	+40	+37	+39†	+42	+33	+47†	+49†	+47	+43

* In the first fourteen cases ¼ drop of compound solution of iodine was given daily; in the last two cases, ½ drop. A indicates admission to the hospital; S, subtotal thyroidectomy, and RH, right hemithyroidectomy.

† represents the time when larger doses (usually 30 drops daily) were started.

‡ Admission was on the 15th day before starting iodine.

§ Admission was on the 20th day, and the basal metabolic rates were +61, +53 and +47 on the 16th, 18th and 17th days, respectively, before starting iodine.

The basal metabolic rates were +83 and +43 on the 27th and 29th days, respectively, after starting iodine. The iodine was then omitted.

TABLE 3.—Summarizing the Effects of the Daily Administration of One-Fifth Drop of Compound Solution of Iodine and of Larger Doses Given Immediately Afterward to Outpatients with Exophthalmic Goiter

Patient	Lab- oratory No.	Age	Height, Cm.	Before Treatment		After Reaching Level on ½ Drop of Compound Solu- tion of Iodine Daily			After Reaching Level on Larger Doses			Total Change in	Comment
				Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Change in Basal Meta- bolic Rate, Points	Basal Meta- bolic Rate, per Cent of Pulse Weight, Normal Rate	Change in Basal Meta- bolic Rate, Points	Size of Dose in Drops Daily				
Miss L. P.	1760	35	157	+37	95	70.1	+29	96	69.5	-8	Following subtotal thyroidectomy
Mrs. M. R.	3913	24	159	+18	80	48.3	+4	67	49.5	-14	-21	-21	Following subtotal thyroidectomy
Mrs. E. C.	4675	35	156	+21	98	48.5	+7	81	48.7	-14	-19	-19	Preceding operation; compound solu- tion of iodine was given previously, but had been omitted for two months
Mrs. E. T.	4906	28	158	+14	80	50.7	+4	72	50.0	-10	-21	-21	Compound solution of iodine was given previously, but had been omitted for four months
Mrs. T. P.	4949	56	149	+20	97	53.8	+11	91	54.6	-9	-14	-14	Compound solution of iodine was given previously, but had been omitted for two months
Mrs. M. P. W.	5004	20	166	+23	96	48.5	+16	82	50.6	-7	-53	-53	Compound solution of iodine was given previously, but had been omitted for one month
Miss D. B.	5053	24	161	+39	127	46.5	+31	115	47.3	-8	No other treatment
Miss S. G.	5092	18	148	+23	101	41.9	+33	100	40.3	+10	+5	+5	No other treatment
Mrs. E. H.	5168	26	164	+48	108	84.5	+51	107	84.1	+3	-19	-19	Preceding operation
Miss M. K.	5181	23	163	+46	115	63.7	+38	108	64.3	-8	+4	+4	Preceding operation
Miss H. J.	5188	19	154	+33	97	56.3	+21	77	56.0	-12	-19	-19	No other treatment
Miss E. M.	5272	35	165	+47	98	60.9	+26	81	63.6	-21	-29	-29	Following subtotal thyroidectomy
Mrs. V. J.	5306	41	163	+21	107	40.5	+11	76	40.9	-10	-19	-19	No other treatment
Miss M. O.	5507	19	155	+37	125	40.7	+31	118	42.9	-6	-21	-21	No other treatment
Mrs. E. O.	5668	52	162	+38	101	57.0	+38	101	56.7	0	-10	-10	No other treatment
All observations (16)....				+32			+24		-8				
All patients receiving large doses (13).....				+31			+23		-8				
Average—All patients in whom the basal metabolic rate dropped 10 points or more; all received large doses (7).....				+28			+15		-13				
							+2		-13				
							+13		-10				
									-18				
									-26				

did the metabolism drop as much as 20 points. In nine of sixteen observations the metabolism did not drop significantly (less than 10 per cent). The average basal metabolic rate before the administration of $\frac{1}{5}$ drop daily was plus 32 per cent; after it had had time to produce a maximum effect, it was plus 24 per cent. In thirteen of the sixteen experiments, larger doses were given immediately after the $\frac{1}{5}$ drop regimen was finished. In these observations the basal metabolic rate was plus 31 per cent before iodine was given, plus 23 per cent after

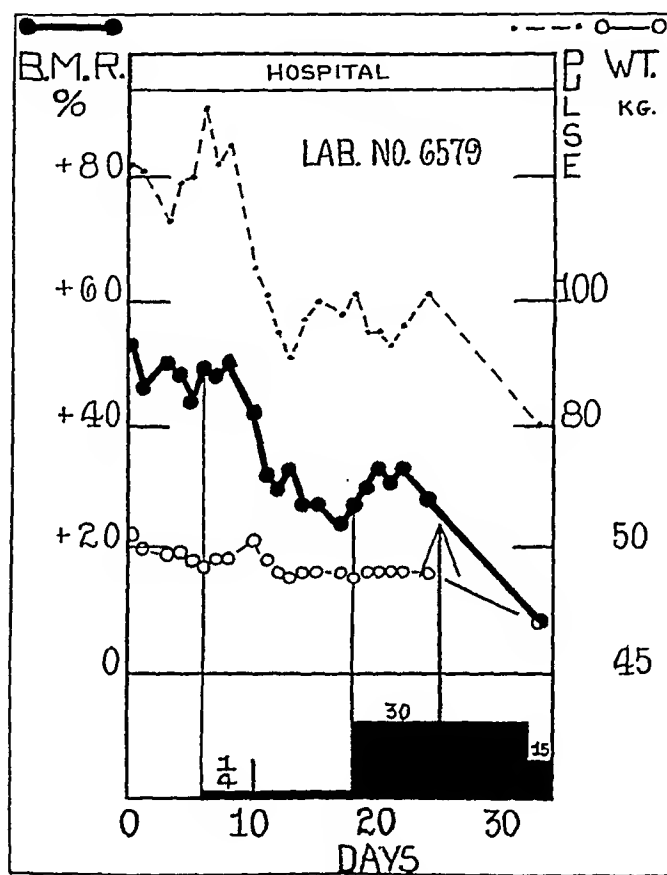


Chart 1.—Moderate reduction in basal metabolism during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter. In this and subsequent charts the arrows denote subtotal thyroidectomies; the black areas represent periods of treatment with compound solution of iodine, and the figures above them the dosage in drops.

$\frac{1}{5}$ drop daily had produced its maximum effect, and plus 13 per cent after larger doses (from 1 to 30 drops daily) had produced their maximum effects. In the seven cases that showed a reduction of 10 points or more during the administration of $\frac{1}{5}$ drop daily, the basal metabolism averaged plus 28 per cent before iodine was begun and plus 15 per cent after this dose had had its maximum effect. The

greatest drop recorded was 21 points (from plus 47 to plus 26 per cent). In chart 8 are given detailed data on an outpatient who showed practically a maximum reduction in basal metabolism on $\frac{1}{5}$ drop daily. This was when the patient had thyrotoxicosis following a subtotal thyroidectomy. Before operation she had shown a marked reduction in basal metabolism on 1 drop daily (table 1 and chart 1 in the first paper of this series¹).

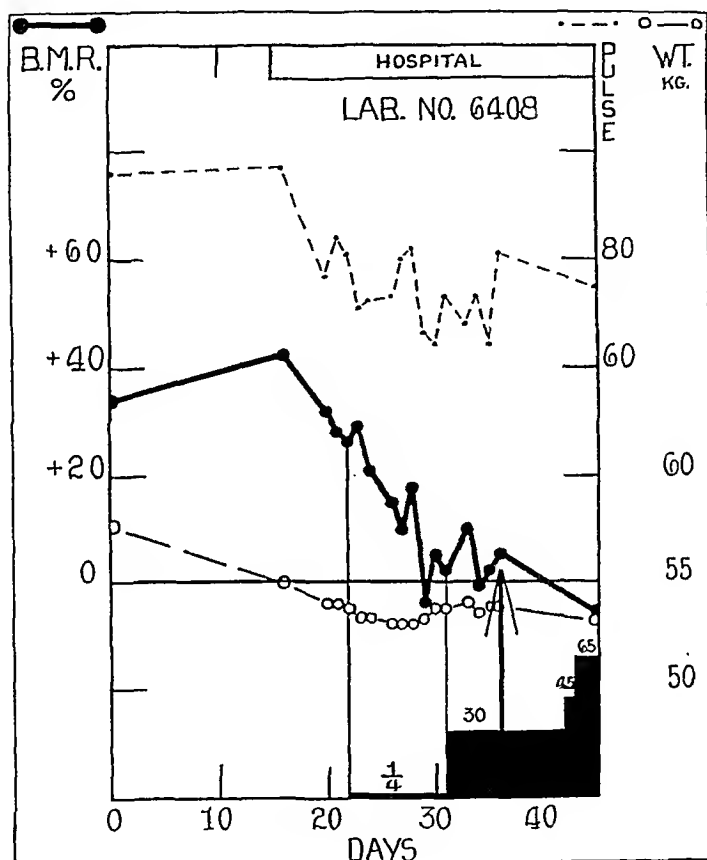


Chart 2.—A reduction in basal metabolism during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily, with no further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

TIME REQUIRED FOR MAXIMUM REDUCTION IN BASAL METABOLISM

The time required for maximum reduction in basal metabolism to occur could be adequately determined only in the house patients who received $\frac{1}{4}$ drop daily. In the seven cases that showed a drop of 10 or more points, the maximum reduction occurred in from three to seven days (five days, on the average). In one of these a drop was noted

within the first twenty-four hours, and in the others it first appeared within from two to four days. In those cases that responded, the average daily drop in the basal metabolic rate was 3.4 per cent—about the same as that in the $\frac{1}{2}$ drop series and a little less than that for the 1 drop series.

COMPARISON OF EFFECTS OF THE ADMINISTRATION OF ONE-QUARTER AND ONE-FIFTH DROP OF COMPOUND SOLUTION OF IODINE DAILY WITH THOSE OF THE ADMINISTRATION OF ONE-HALF AND ONE DROP DAILY

In table 4 and chart 9 we have compared the effects on basal metabolism, of administering 1, $\frac{1}{2}$ and $\frac{1}{4}$ drops, respectively, of com-

TABLE 4.—*Comparison of the Effect on Basal Metabolism of the Daily Administration of One Drop, One-Half Drop, One-Fourth Drop and One-Fifth Drop of Compound Solution of Iodine to Hospital Patients with Exophthalmic Goiter*

Series	Num- ber of Cases	Average Basal Metabolic Rate, per Cent of Normal				On Small Doses		Aver- age Total Drop in Basal Meta- bolic Rate on All Doses, Points	Aver- age Drop in Basal Meta- bolic Rate on Small Doses, Points
		On Admis- sion	Rest- ing Level	After	After	Great- est Drop in Basal Meta- bolic Rate; Points	Aver- age Drop in Basal Meta- bolic Rate, Points		
				Reach- ing a Level on Small Doses	Reach- ing a Level on Larger Doses				
1 drop (all cases).....	17	+60	+46	+19	49	27
1 drop (cases that responded)*	15	+64	+50	+19	49	31	..	4.4
1 drop (cases in which larger doses were given).....	14	+62	+48	+19	+21	49	29	27	...
1 drop (cases that responded and that also were given larger doses)	12	+67	+52	+20	+22	49	32	30	...
$\frac{1}{2}$ drop (all cases).....	20	+54	+40	+26	+21	40	14	19	...
$\frac{1}{2}$ drop (cases that responded)	13	+53	+42	+18	+17	40	24	25	3.4
$\frac{1}{4}$ drop (all cases).....	14	+62	+43	+34	+29	26	9	14	...
$\frac{1}{4}$ drop (cases that responded)	7	+63	+42	+25	+21	26	17	21	3.4
$\frac{1}{5}$ drop (all cases).....	2	+58	+47	+41	+42	14	6	5	...
$\frac{1}{5}$ drop (case that responded)	1	+51	+53	+39	+41	14	14	12	...

* A response means a drop of 10 points or more in the basal metabolic rate.

pound solution of iodine daily in three series of hospital patients with exophthalmic goiter. In all series the cases were unselected and the disease was of about the same general severity. All observations were made under approximately the same conditions. The results, therefore, are comparable. They show that:

1. The percentage of cases that responded was least in the $\frac{1}{4}$ drop series—50 per cent as compared with 65 per cent for the $\frac{1}{2}$ drop series and 88 per cent for the 1 drop series.

2. The average response was least in the $\frac{1}{4}$ drop series—9 points (from plus 43 to plus 34 per cent) as compared with 14 points (from plus 40 to plus 26 per cent) in the $\frac{1}{2}$ drop series and 27 points (from plus 46 to plus 19 per cent) in the 1 drop series.

3. When only the cases that showed a reduction in basal metabolism are considered in each series, the response was least in the $\frac{1}{4}$ drop series. Thus in this series, seven cases that responded showed an average reduction of 17 points (plus 42 to plus 25 per cent) in basal metabolism, whereas in the $\frac{1}{2}$ drop series, the thirteen cases that responded showed an average reduction of 24 points (from plus 42 to plus 18 per cent), and in the 1 drop series, the fifteen cases that responded showed an average reduction of 31 points (from plus 50 to

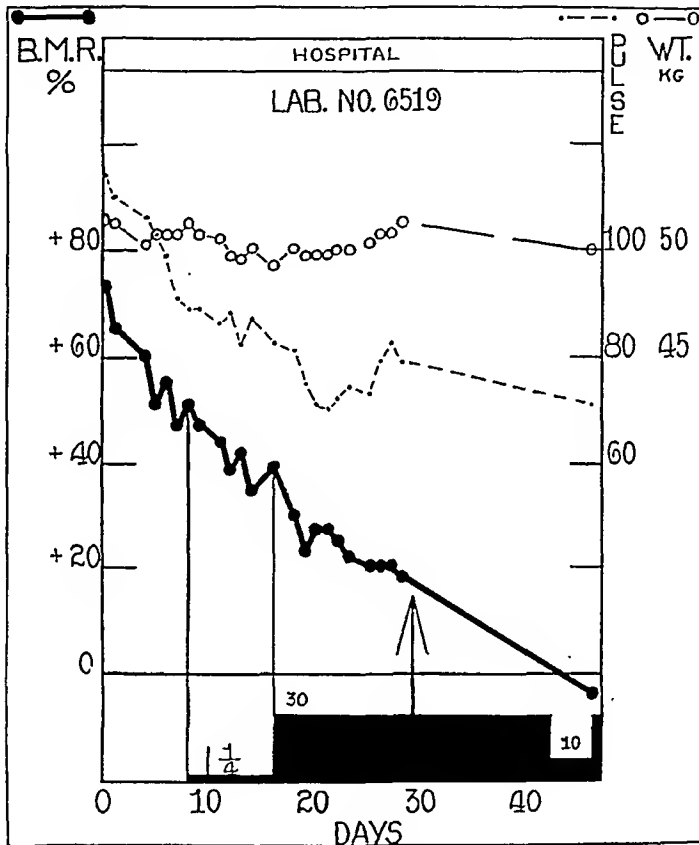


Chart 3.—A reduction in basal metabolism during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily, with some further reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

plus 19 per cent). A relation between the amount of the reduction in basal metabolism and the size of the dose can be shown also in a few cases of the disease in which the preliminary administration of small doses did not completely interfere with the effect of larger doses subsequently administered. Thus case 5168 in table 3 showed no response on $\frac{1}{5}$ drop, a moderate response on 1 drop and a maximum on 5 drops.

The foregoing comparison might not be considered entirely fair, as it means comparing seven cases in the $\frac{1}{4}$ drop series with thirteen in

the $\frac{1}{2}$ drop series and fifteen in the 1 drop series. In only one, however, of the fifteen cases that responded in the 1 drop series did the basal metabolism drop less than 20 points. Thus, the average reduction of the seven cases in the 1 drop series that showed the smallest response (i. e., 10 or more points) is greater than the average for the seven of the $\frac{1}{4}$ drop series that responded. There can be little doubt, therefore, that there is a difference in the magnitude of the response in those

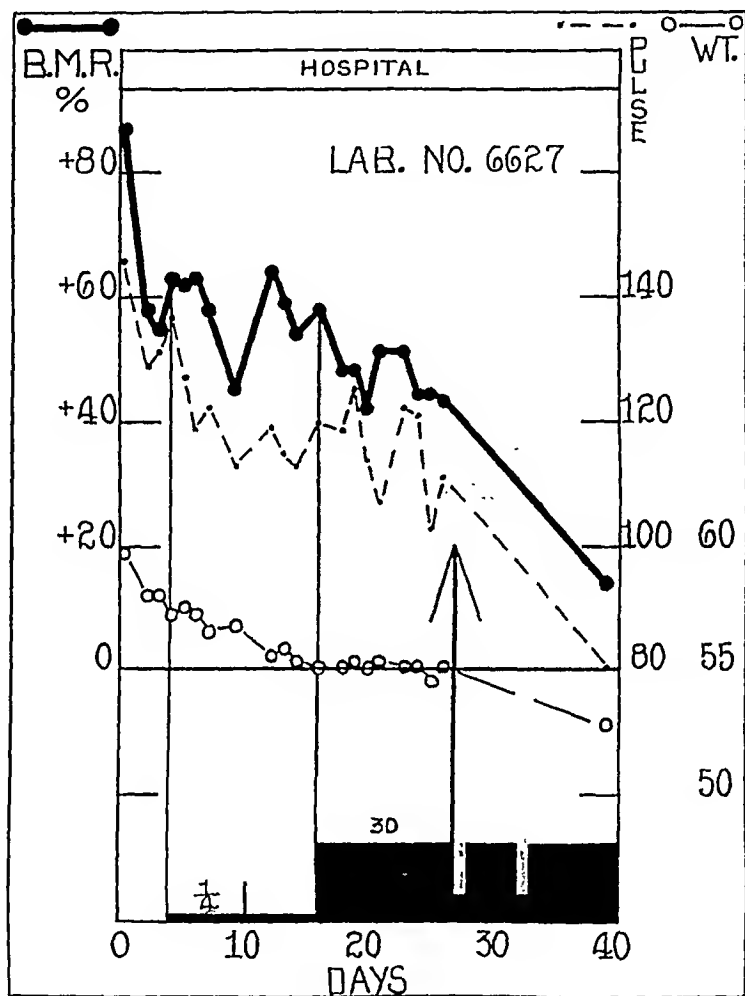


Chart 4.—No reduction in basal metabolism during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily followed by a slight reduction during the administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

that responded in the two series. This is also suggested by the fact that the greatest reduction in the 1 drop series was 49 points, in the $\frac{1}{2}$ drop series 40 points, and in the $\frac{1}{4}$ drop series 26 points.

4. Not only was the response to $\frac{1}{4}$ drop less than that to $\frac{1}{2}$ and 1 drop, but the total reduction in basal metabolism on all doses of iodine

was less in the $\frac{1}{4}$ drop series than in the other two. Thus, the effect of all doses in the $\frac{1}{4}$ drop series was to reduce the basal metabolic rate only 14 points (from plus 43 to plus 29 per cent), as compared with 19 points (from plus 40 to plus 21 per cent) in the $\frac{1}{2}$ drop series and 27 points (from plus 48 to plus 21 per cent) in the 1 drop series. (This refers only to those patients who received large doses.)

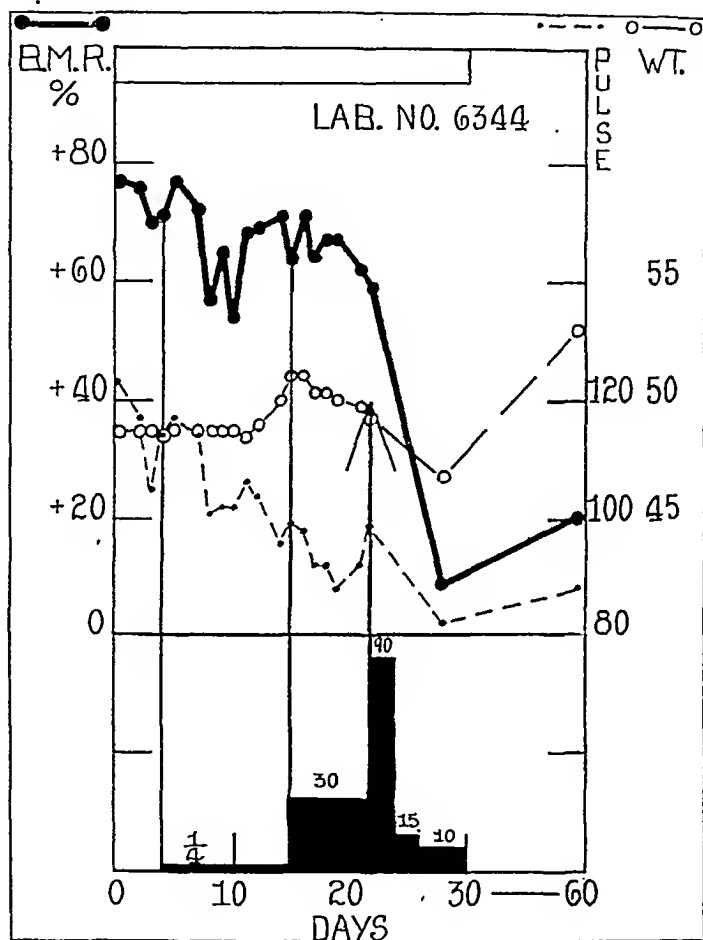


Chart 5.—No reduction in basal metabolism either during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily or during the subsequent administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

As previously pointed out, the difference between the effects of large doses in the $\frac{1}{2}$ and 1 drop series could be accounted for by the fact that in the former the large doses were not given long enough to produce their maximum effects. The small effect of large doses in some of the cases in the $\frac{1}{4}$ drop series can perhaps be explained in a similar manner. It seems unlikely that it can be explained so simply in all of them, however. Thus, in the nine cases (6344, 6519, 6537,

6539, 6542, 6579, 6586, 6627 and 6634) in the $\frac{1}{4}$ drop series in which 30 drops a day were given for six to twelve days (average, eight days) immediately after the small dose, the results were no more satisfactory than in the cases in which the large dose was given for a shorter time. The average basal metabolic rate of these nine patients on admission was plus 68 per cent; the average resting rate was plus 49 per cent; after $\frac{1}{4}$ drop had been given daily for an average of eleven and one-half days it was plus 43 per cent, and on 30 drops a day it decreased

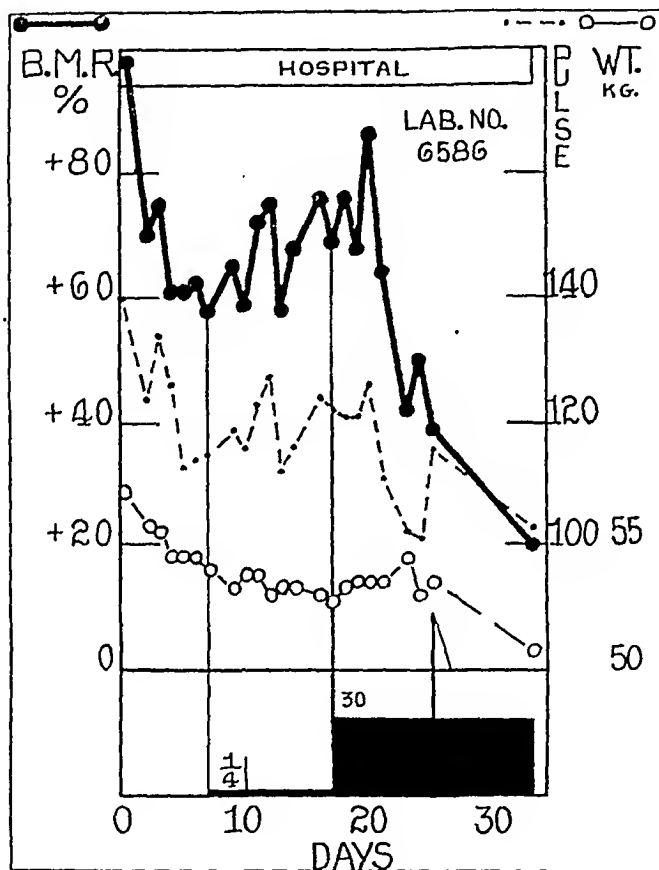


Chart 6.—A rise in basal metabolism and an increase in severity of exophthalmic goiter during the administration of $\frac{1}{4}$ drop of compound solution of iodine daily followed by a reduction in both factors during the administration of 30 drops daily, preceding a hemithyroidectomy (represented by half arrow).

only to plus 35 per cent. In seven of the cases (6344, 6413, 6423, 6537, 6542, 6586 and 6627) that showed no reduction in basal metabolism during the administration of $\frac{1}{4}$ drop, a reduction on 30 drops a day was noted only in two, and in these two it was not great. In these seven cases the large doses were given for an average of seven days after the small dose.

The conclusion is thus suggested that doses of iodine that are too small to affect the basal metabolism or that are so small as to have

only a slight effect, may in some way interfere with the effect of larger doses subsequently administered.⁴

Although the effect of $\frac{1}{5}$ drop was observed on only two house patients, the data on them so far as they go, support this conclusion (table 1). It is doubtful whether the conclusion is upheld by the data on the outpatients who received $\frac{1}{5}$ drop, and it does not appear to be upheld by the data thus far collected on the effect of administering $\frac{1}{8}$ drop daily to house patients. The average reduction on all doses, in patients who received large doses, was roughly the same in both the

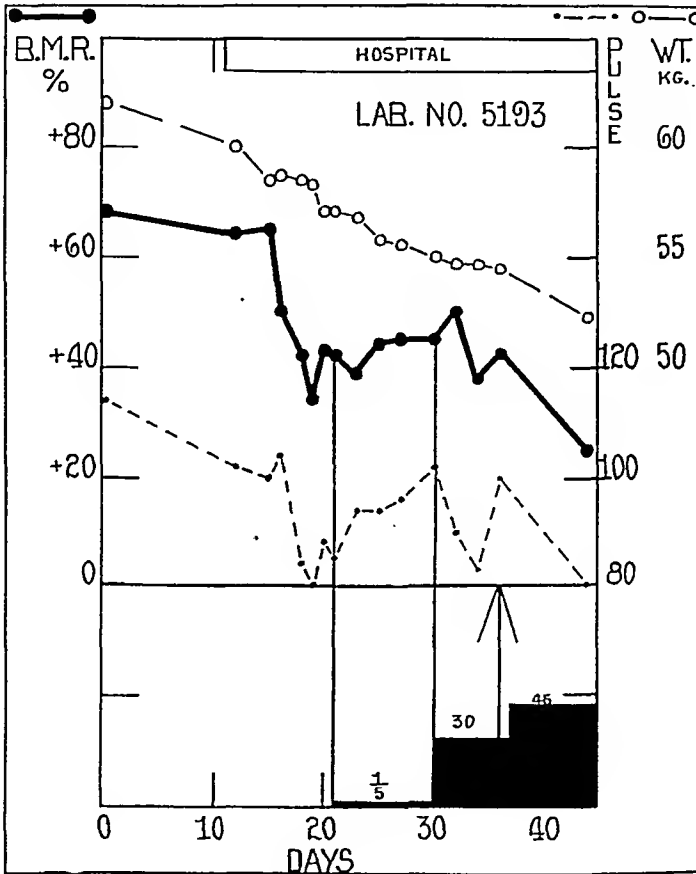


Chart 7.—No reduction in basal metabolism either during the administration of $\frac{1}{5}$ drop of compound solution of iodine daily or during the subsequent administration of 30 drops daily, preceding a subtotal thyroidectomy for exophthalmic goiter.

4. To date, there has been one postoperative death in the patients in this study (no. 5850 of the $\frac{1}{2}$ drop series). This patient died suddenly, about forty hours after an uneventful subtotal thyroidectomy. We consider it unlikely that the small dose given before the large dose was responsible for his death because, although his disease was initially severe, his basal metabolism dropped to plus 27 per cent on administration of iodine, and he appeared to be a satisfactory operative risk. The cause of death was undetermined but was thought to be a pulmonary embolus. We have not made a systematic study to determine whether the immediate postoperative reaction in these patients was more severe than that in a group of patients given large doses initially.

$\frac{1}{8}$ and the 1 drop series of outpatients (chart 10). Practically all the outpatients, however, had the disease in mild form. It has been our experience that such cases are in general more labile to iodine than are severe cases. Thus we held the disease in check for years in a small series of mild cases of the disease by the continuous administration of iodine, whereas in severe cases with similar medication, the disease practically always became worse—usually after a short period of “remission.”⁵

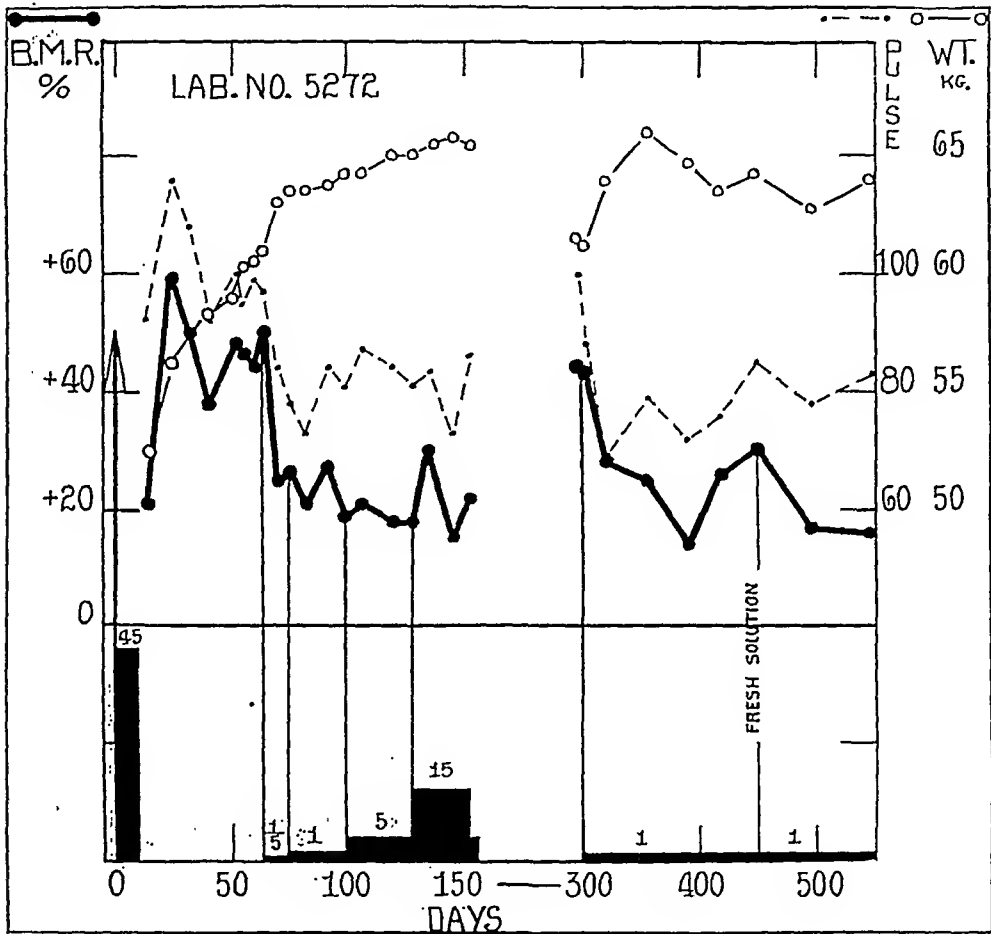


Chart 8.—Maximum reduction in basal metabolism during the daily administration of $\frac{1}{8}$ drop of compound solution of iodine to a patient who had thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter.

In six house patients in whom we have thus far observed the effect of the daily administration of $\frac{1}{8}$ drop of compound solution of iodine, this small dose, while having little effect in itself, did not seem to interfere with the effect of the large dose given immediately afterward. Thus, the average basal metabolic rate on admission was plus 55 per cent; after a period of rest, it was plus 41 per cent; after $\frac{1}{8}$ drop had

5. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Some Experiences with the Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, *Arch. Int. Med.*, in press.

been given daily for an average of twelve days, it was plus 36 per cent; and on 30 drops a day, it dropped to plus 14 per cent. While the effect of large doses was observed for nine to sixteen days, or for an average of twelve days, the lowest level of metabolism during their administration appeared in from three to ten days, or in an average of six days. It thus appears unlikely that an inadequate period of observation could account for the small effect of large doses in the nine cases in the $\frac{1}{4}$ drop series in which their effect was noted for from six to twelve days (average, eight days). Although the patients in the $\frac{1}{4}$ drop series appeared, on the whole, to have the disease in more severe form than

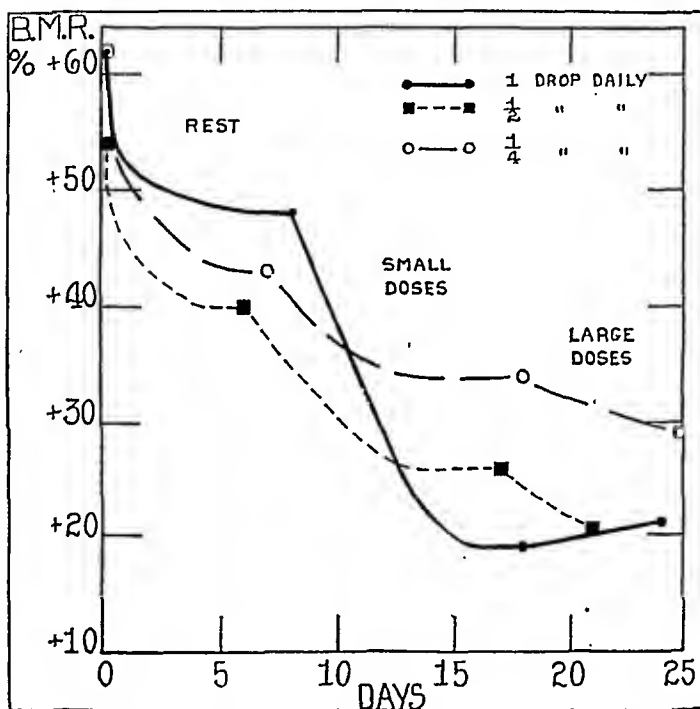


Chart 9.—A comparison of the effects on basal metabolism of the daily administration of 1, $\frac{1}{2}$ and $\frac{1}{4}$ drop, respectively, of compound solution of iodine to three series of hospital patients. In each case the first point is the average of the basal metabolisms shortly after admission; the second point is the average resting level of metabolism; the third point is the average of the levels to which the metabolism fell during the administration of small doses ($\frac{1}{4}$, $\frac{1}{2}$ and 1 drop daily), and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually 30 drops daily). Only those cases are considered in which the effect of larger doses was noted. The points are arbitrarily connected by curved lines, as these denote the true course of the basal metabolism more nearly than straight lines.

those thus far included in the $\frac{1}{8}$ drop series, the reason for the difference in the response of these two series of patients to large doses is by no means clear. It is possible that the difference in the small doses of iodine may be important, and the $\frac{1}{8}$ drop series is perhaps too small

at present to draw conclusions from. Then, of course, it must be recognized that the effect of giving large doses of iodine initially to these two groups of patients instead of preceding their administration by that of small doses, is unknown.

The effect of administering $\frac{1}{5}$ drop of compound solution of iodine to outpatients is compared with that of administering 1 drop in table 5 and chart 10. In both groups, most of the patients had the disease in mild form, and the average level of basal metabolism was about the same in both before iodine was started. The metabolic rate decreased, on the average, only 8 points (from plus 32 to plus 24 per cent) on $\frac{1}{5}$ drop, but it was reduced, on the average, 21 points (from plus 32 to plus 11 per cent) by 1 drop. The maximum reduction in the $\frac{1}{5}$ drop series was 21 points (from plus 47 to plus 26 per cent) as compared

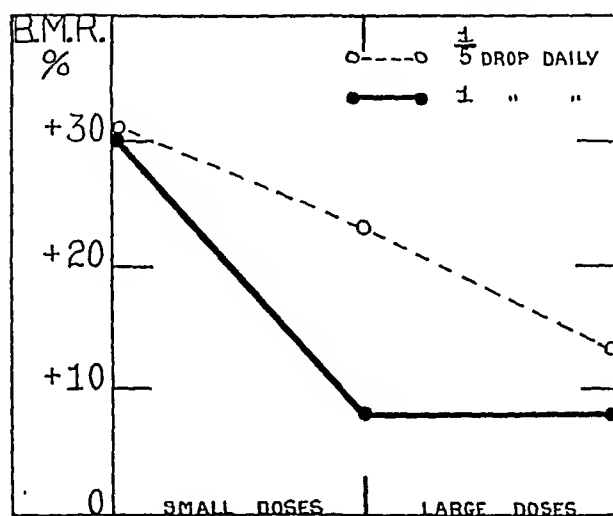


Chart 10.—A comparison of the effects on basal metabolism of the daily administration of 1 drop and $\frac{1}{5}$ drop of compound solution of iodine to two series of outpatients.

with 44 points (from plus 72 to plus 28 per cent) in the 1 drop series. The difference is still striking if in each series only the cases are considered in which the metabolism dropped 10 points or more. In seven such observations on $\frac{1}{5}$ drop, the basal metabolic rate was lowered, on the average, 13 points (from plus 28 to plus 15 per cent), whereas in twenty-three observations on 1 drop it was lowered, on the average, 26 points (from plus 33 to plus 7 per cent). In the 1 drop series no further lowering of the metabolism was usually noted when the dose of iodine was markedly increased, whereas in the $\frac{1}{5}$ drop series it averaged 10 points lower on large doses.

The difference in effect between $\frac{1}{5}$ drop and 1 drop of compound solution of iodine daily in the outpatients, merely serves to confirm the differences between the effects of $\frac{1}{4}$, $\frac{1}{2}$ and 1 drop in the three series of house patients.

COMMENT

From the data presented, it is obvious that the effect of iodine on the basal metabolism in exophthalmic goiter is not of the all-or-none type, but that it is related within certain limits to the size of the dose. In most cases seen in this hospital, the minimum amount of iodine that will produce a maximum reduction in basal metabolism is about 6 mg. per day, whereas the smallest dose that will produce any reduction is a little greater than 1.5 mg. per day in about 50 per cent of the cases. As the upper and lower limits vary considerably from case to case, the actual range in many instances is probably somewhat less than the foregoing figures would indicate.

TABLE 5.—*Comparison of the Effect on Basal Metabolism of the Daily Administration of One Drop and of One-Fifth Drop of Compound Solution of Iodine to Outpatients with Exophthalmic Goiter*

Series	Number of Observations	Before Treatment	Average Basal Metabolic Rate, per Cent of Normal		On Small Doses		Average Total Drop in Basal Metabolic Rate on All Doses, Points
			After Reaching a Level on Small Doses	After Reaching a Level on Large Doses	Greatest Drop in Basal Metabolic Rate, Points	Average Drop in Basal Metabolic Rate, Points	
1 drop (all cases).....	28	+32	+11	44	21	..
1 drop (cases on larger doses).....	15	+30	+ 8	+ 8	44	22	22
1 drop (all cases that responded)*.....	23	+33	+ 7	44	26	..
1 drop (all cases that responded and also had larger doses).....	13	+31	+ 6	+ 6	44	25	25
1/5 drop (all cases).....	16	+32	+24	21	8	..
1/5 drop (cases on larger doses).....	13	+31	+23	+13	21	8	18
1/5 drop (all cases that responded; all had larger doses)	7	+28	+15	+ 2	21	13	26

* A response means a drop of 10 points or more in the basal metabolic rate.

It is well known that typically, the reduction in basal metabolism during the administration of iodine in exophthalmic goiter is accompanied by a storage of colloid and an increase in the size of the thyroid gland.⁶ It would appear reasonable to try to find some correlation between the amount of iodine necessary to cause a marked storage of colloid and the amount necessary to cause a maximum reduction in

6. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment, Arch. Int. Med. 8:265 (Sept. 15) 1911. Cattell, R. B.: The Pathology of Exophthalmic Goitre: A Histological and Chemical Study of the Changes Following the Administration of Iodin (Lugol's Solution), Boston M. & S. J. 192:989, 1925. Rienhoff, W. F., Jr.: The Histological Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine, Bull. Johns Hopkins Hosp. 37:285, 1925.

basal metabolism. In a consideration of our data from this point of view it must be recognized that there are at least three unknown quantities: (1) the amount of iodine excreted unused on the doses given, (2) the amount of iodine present in the gland before treatment was started and (3) the capacity of the gland to store iodine.

There is some evidence bearing on these three points. Marine⁷ has presented data which suggest that when a small amount of iodine is administered, a large part of it may be absorbed by the thyroid gland. When a great excess is given, however, most of it is eliminated in the urine within twenty-four hours (Cattell⁸ and Greenbaum, and Raiziss⁹). In the literature there are a few reports on the iodine content of exophthalmic goiter glands from patients who had been operated on without receiving iodine, as compared with those who had received iodine.¹⁰

From the weight of the portion of gland removed at operation and the fraction that this formed of the whole gland, it is possible to calculate roughly the weight of the thyroid at the time of operation. The average weight of the whole gland in thirty-two of our cases (all four series of house patients) was thus calculated to be about 82 Gm.¹¹ Marine and Lenhart,¹² in Cleveland, found an average iodine content of 1.14 mg. per gram of dried gland in fifty-eight patients with exophthalmic goiter who did not receive iodine, and an average of 3.08 mg. per gram in eight patients who received iodine. Before the days of iodine medication in exophthalmic goiter, Wilson and Kendall¹³ found an average iodine content of 0.96 mg. per gram of dried gland in one

7. Marine, D.: Etiology and Prevention of Simple Goiter, *Medicine* **3**:453, 1924.

8. Cattell, R. B.: The Elimination of the Iodine in the Urine in Normal Persons and in Exophthalmic Goiter, *Boston M. & S. J.* **195**:69, 1926.

9. Greenbaum, F. R., and Raiziss, G. W.: Elimination of Iodine After Oral or Intravenous Administration of Various Iodine Compounds in Single Massive Doses, *J. Pharmacol. & Exper. Therap.* **30**:407, 1927.

10. Marine and Lenhart (footnote 6, first reference). Cattell (footnote 6, second reference). Wilson, L. B., and Kendall, E. C.: The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, *Am. J. M. Sc.* **178**:79, 1916. Weir, J. F.: The Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, and the Iodin Compounds in Desiccated Thyroid, *Am. J. M. Sc.* **169**:860, 1925.

11. It is perhaps best from the point of view of the general problem to take the average of all glands weighed, because in the 1 drop series several of the lighter glands were not weighed and in the $\frac{1}{4}$ drop series two of the heavier ones were not. (If all thyroid glands in all series had been weighed, the average weight for each series would have been more nearly equal.)

12. Marine and Lenhart (footnote 6, first reference).

13. Wilson and Kendall (footnote 10, third reference).

hundred and thirty-seven cases at the Mayo Clinic. After iodine was introduced, Weir,¹⁴ working at the same Clinic, found an average iodine content of 2.58 mg. per gram in twenty-four cases. The corresponding figures reported by Cattell¹⁵ from the Lahey Clinic in Boston are 2.1 mg. (fourteen cases) and 4.2 mg. (sixteen cases), respectively. Assuming the ratio of dry to wet weight to be about one-fifth, the thyroid glands of our patients, on the basis of the figures of Marine and Lenhart, would have contained 18.7 mg. of iodine before medication was started and 50.5 mg. after iodine was administered—a difference of 31.8 mg.; on the basis of the figures reported from the Mayo Clinic, 15.7 mg. and 42.3 mg., respectively—a difference of 26.6 mg.; and on the basis of Cattell's figures, 34.4 mg. and 68.9 mg., respectively—a difference of 34.5 mg. In our 1 drop series, 42 mg. of iodine were supplied to each patient in seven days—the average time required for a maximum reduction in basal metabolism to appear. During the same time, on a daily dose of $\frac{1}{2}$ drop and $\frac{1}{4}$ drop of compound solution of iodine, only 21 mg. and 10.5 mg. of iodine, respectively, were supplied to each patient. Thus, in seven days on the smaller doses ($\frac{1}{2}$ and $\frac{1}{4}$ drop), sufficient iodine was not supplied for the maximum storage of colloid even if it could all be used for that purpose. Moreover, even on these small doses it seems probable that some iodine would be eliminated unused. The actual portion of them that would be utilized is unknown, but it is doubtful if, on 1 drop a day, it would be any larger than the minimum required for maximum storage.

The reason for the maximum effect of 1 drop and the less marked effect of smaller doses, therefore, may be that 1 drop a day is roughly about the minimum dose that enables the gland in most cases to store colloid at an adequate rate. It is thus of interest that the few patients who showed a reduction in basal metabolic rate during the administration of $\frac{1}{4}$ drop daily had the disease in mild form. It is at present unknown, of course, whether it is necessary to have a maximum storage of colloid in order to have a maximum reduction in basal metabolism.

A further analysis of the data suggests that the smaller the gland the less the amount of iodine required to produce a reduction in basal metabolism. Whereas two patients, whose thyroid glands weighed more than 200 Gm., showed a well marked reduction in basal metabolism during the administration of 1 drop of compound solution of iodine daily, no patient whose thyroid weighed more than 84 Gm. showed a reduction in basal metabolism during the administration of $\frac{1}{2}$ drop a day, and no patient whose thyroid weighed more than 34 Gm. showed a reduction during the administration of $\frac{1}{4}$ drop a day (except one

14. Weir (footnote 10, fourth reference).

15. Cattell (footnote 6, second reference).

whose thyroid weighed 154 Gm. and whose metabolism dropped only 10 points).

A similar conclusion is suggested by table 6. Thus, if all $\frac{1}{2}$ drop cases in which the gland was weighed are considered, the average theoretical maximum amount of iodine available for the storage of colloid (the amount of iodine administered plus the iodine content of the gland before medication was started) was considerably less than the amount which the gland could hold. The reduction in basal metabolism was correspondingly small—only 10 points (from plus 39 to plus 29 per cent). On the other hand, in the seven cases in the $\frac{1}{2}$ drop series in which the thyroid was weighed and a reduction in basal metabolism was noted, the theoretical amount of iodine available for the storage of colloid more nearly approached the amount that the gland could hold. In these cases the average reduction in basal metabolism was well marked—23 points (from plus 39 to plus 16 per cent). A similar situation existed in the $\frac{1}{4}$ drop series,

While the average weight of the glands in the 1 drop series was greater than that of the glands in the $\frac{1}{2}$ and $\frac{1}{4}$ drop series, the theoretical amount of iodine available for the storage of colloid was proportionately greater in the 1 drop series than in the other two, and the average reduction in basal metabolism was correspondingly greater. In the four cases in the $\frac{1}{4}$ drop series in which the weight of the thyroid was determined and in which there was a reduction of basal metabolism of more than 10 points, the ratio of iodine available for colloid storage to the amount of iodine that the gland could hold was less than in the 1 drop series, and the reduction in basal metabolism was also less.

There are, however, certain discrepancies when an attempt is made to explain the reduction in basal metabolism entirely on the basis of storage of colloid. In the two cases in the $\frac{1}{2}$ drop series in which the thyroid weighed over 80 Gm. (actual weights, 81 and 84 Gm.) and a well marked reduction in basal metabolism occurred, and in the two cases in the 1 drop series in which the thyroid weighed more than 200 Gm. and a reduction in basal metabolism occurred, the amount of iodine supplied to the patients on the small dose regimens would certainly not have been adequate to cause a maximum storage of colloid unless the iodine content of the gland had been high before medication was started. Moreover, the reduction in basal metabolism presumably can begin before much colloid is stored; e. g., in five patients of the 1 drop series, four of the $\frac{1}{2}$ drop series and one of the $\frac{1}{4}$ drop series, it had started within twenty-four hours. Some of these patients had large thyroid glands. It would thus appear that the output of thyroxin is sometimes diminished before sufficient colloid can be stored to produce a mechanical

TABLE 6.—Summary of Relationship Between the Estimated Iodine Capacity of the Thyroid and the Theoretical Amount of Iodine Available for Storage (of Colloid) by This Gland on the Various Doses Administered

Possible Iodine Content of Thyroid Glands in Our Series																
Num- ber of Cases	Aver- age Weight of Thyroid Gland, Gm.	Average Amount Time of Admin- istered Iodine Maxi- mum Reduc- tion in Time Required Basal Meta- bolic Rate, Days	On Basis of Figures of Marine and Lenhart			On Basis of Mayo Clinic Figures			On Basis of Cattell's Figures			Sum of Iodine Adminis- tered and Iodine in Gland			Average Basal Metabolic Rate, per Cent of Normal	Drop in Basal Meta- bolic Rate, Points
			Before Iodine Medi- cation, Mg.	After Iodine Medi- cation, Mg.	Sum of Iodine Adminis- tered and Iodine in Gland	Before Iodine Medi- cation, Mg.	After Iodine Medi- cation, Mg.	Sum of Iodine Adminis- tered and Iodine in Gland	Before Iodine Medi- cation, Mg.	After Iodine Medi- cation, Mg.	Sum of Iodine Adminis- tered and Iodine in Gland					
All 1 drop cases in which thy- roid was weighed; all re- sponded to iodine.....	8	111	7	42	25.3	68.3	67.3	21.4	57.3	63.4	46.6	93.2	88.6	+51	+19	33
All 1/4 drop cases in which thyroid was weighed.....	12	77	7	21	17.6	47.4	38.6	14.8	39.7	35.8	32.3	64.7	53.3	+39	+23	11
All the foregoing 1/2 drop cases that responded to iodine....	8	49	6	18	11.2	30.2	29.2	9.4	25.3	27.4	20.6	41.2	38.6	+41	+18	23
All 1/4 drop cases in which thyroid was weighed.....	11	57	5	7.5	13.0	35.1	20.5	10.9	29.4	18.4	23.9	47.8	31.4	+42	+33	9
All the foregoing 1/4 drop cases in which the basal metabolic rate dropped 10 or more points on iodine.....	5	54	4	6.0	12.3	33.3	18.3	10.4	27.8	16.4	22.7	45.3	28.7	+41	+24	17
All the foregoing 1/4 drop cases in which the basal metabolic rate dropped more than 10 points*	4	29	4	6.0	6.6	17.9	12.6	5.6	15.0	11.6	12.2	24.4	18.2	+40	+21	19
The 1/2 drop case in which thyroid was weighed.....	1	200	1	1.2	45.6	123.2	46.8	38.4	113.2	59.6	84.0	108.0	85.2	+53	+39	14

* These two subdivisions of the 1/2 drop data are made because, by including among those that responded to iodine, the one case (no. 6539) in which the thyroid weighed 154 Gm. and in which the metabolism dropped only 10 points on 1/4 drop, the average weight of the thyroid in such cases is practically doubled (54 instead of 29 Gm.), and the difference between the iodine capacity of the gland and the theoretical amount of iodine available for storage (of colloid) is markedly increased.

blocking of the secretion according to Marine's theory.¹⁶ These considerations have led us to wonder whether storage of colloid is the cause of, or merely an accompaniment of, the fundamental change which iodine produces in the thyroid gland of exophthalmic goiter.

It is impossible to determine whether, when a reduction in basal metabolism occurs, any of the iodine administered is utilized in the elaboration of thyroxin. It is conceivable, however, that when the disease is acting with great intensity, the thyroid may thus utilize so much iodine that 1 drop daily is not sufficient to cause an adequate storage of colloid and, therefore, does not produce a maximum effect. It is doubtful if in exophthalmic goiter there is ever produced an excess of thyroxin which requires more than 6 mg. of iodine daily in its elaboration (at least thirty-eight times the daily output of a normal thyroid gland). In support of this is the fact that we have not yet observed a patient who failed to show some response to a dose of 1 drop daily that showed any response to any dose. Thus, on theoretical grounds, we doubt if the dose required to produce a maximum effect is ever greater than 5 drops of compound solution of iodine daily, and it may be less than this in all cases.

As the daily amount of iodine necessary to keep the thyroid gland of a normal man in a healthy state is probably much less than 0.16 mg. per day,¹ the amount that must be supplied to a patient with exophthalmic goiter before any reduction in basal metabolic rate will occur (a little over 1.5 mg. in about 50 per cent of the cases) is greater than would be necessary to supply a marked excess of thyroxin, if it were all utilized for that purpose. Our data thus suggest that iodine must be supplied to the thyroid faster than it can be utilized in the elaboration of thyroxin in order to produce the functional change that is associated with the storage of colloid and a decrease in the output of the hormone. Whether or not the thyroid can utilize iodine to form a still greater excess of thyroxin when it is not given fast enough to cause a storage of colloid is a difficult problem. From this standpoint, the increase in basal metabolism in two of the cases in our $\frac{1}{2}$ drop series (charts 5 and 6 in the second paper of this series²) and in one of the cases in our $\frac{1}{4}$ drop series (chart 6) is of interest. In these three cases, the

16. Marine, D.: *Iodin in the Treatment of Diseases of the Thyroid Gland*, *Medicine* 6:127, 1927. While Marine and Rogoff (*J. Pharmacol. & Exper. Therap.* 9:1, 1916-1917) have shown that an increased deposit of colloid can be detected in the thyroid glands of normal animals as early as twenty hours after the administration of a single large dose of iodine, 1.5 to 6 mg. of iodine is probably inadequate to cause enough storage of colloid to produce "pressure retention," even if all of it could be used for this purpose within twenty-four hours. It may be maintained, of course, that a sudden small increase in the amount of colloid is sufficient to initiate the change.

reaction to iodine appeared to be reversible, the administration of small doses being associated with an increase in the basal metabolism and severity of the disease, and the immediate subsequent administration of large doses being associated with a decrease in both factors. The rise and fall corresponded so well with the administration of small and large doses of iodine, respectively, that it seems unlikely that the phenomenon can be explained entirely on the basis of the spontaneous course of the disease. It is of interest that in all three cases the thyroid gland was large, the weight varying from 107 to 164 Gm.

It would not be surprising if in cases in which the cause of the disease is acting with great intensity, the gland could use as much as 3 mg. of iodine daily in the elaboration of thyroxin. If this explanation is correct, it may seem peculiar that more of the cases that did not show a reduction in basal metabolism in the two series, did not show a rise. There are at least three possible explanations for this: 1. It may be necessary to administer the iodine at a time when the disease is set to increase in severity spontaneously.¹⁷ 2. In most of the cases the gland may have been secreting thyroxin at a maximum rate regardless of the iodine intake, salvaging, if necessary, the iodine atoms from the breakdown of thyroxin. 3. Sufficient time may not have elapsed for the extra thyroxin that could be produced to affect the metabolism. In a period of ten days in the $\frac{1}{4}$ drop series, 15 mg. of iodine would be the maximum available for the production of thyroxin. If all of this iodine could be utilized without loss in the elaboration of thyroxin, 23 mg. of the hormone would be produced. It would not be surprising if in some cases longer than ten days is necessary for 2.3 mg. of thyroxin daily to affect the basal metabolism when it is already high. While this is a plausible explanation for the cases in the $\frac{1}{4}$ drop series, it is doubtful if it is adequate to explain the lack of increase in the cases in the

17. Observations that we made on the effect of the prolonged treatment of the disease with iodine alone (footnote 5) have led us to believe that the rôle of iodine during an increase in the severity of exophthalmic goiter may be in large part a passive one, the iodine administered representing an excess of one of the raw materials out of which a still greater excess of thyroxin may be made. The idea that the spontaneous course of the disease is the most important thing in determining variations in the response of patients with exophthalmic goiter to iodine was expressed in an article by Means, Thompson and Thompson (*Tr. A. Am. Phys.* 43:146, 1928) and by Means and Richardson (*Diseases of the Thyroid*, New York, Oxford University Press, 1929, p. 151). We have also noted, however, that during the continuous administration of iodine its effect may wear off at least in part. Thus, in the presence of an excess of this element, it would often appear that some reaction occurs which tends to counteract its beneficial effect. This phenomenon corresponds so closely with the administration of iodine that it seems unlikely that it can be explained satisfactorily by the spontaneous course of the disease. We therefore think it unwise to consider that the rôle of iodine during such an increase in the severity of exophthalmic goiter is entirely passive.

$\frac{1}{2}$ drop series, in which a possible maximum of 4.6 mg. of thyroxin daily could be produced from the iodine administered.

It is of some interest that in the cases which responded in the $\frac{1}{4}$ drop and in the $\frac{1}{2}$ drop series, the maximum reduction in basal metabolism occurred just as quickly as in the 1 drop series. It occurred in five days on the average in the $\frac{1}{4}$ drop series and in seven days in the $\frac{1}{2}$ and 1 drop series. Thus, it may be seen from table 4 that the average daily rate of reduction in basal metabolism in the cases that responded was 4.4, 3.4 and 3.4 points, respectively, for the 1, $\frac{1}{2}$ and $\frac{1}{4}$ drop series. It seems surprising, perhaps, that on the smaller doses the slower rate of reduction did not persist for a longer time, so that the total reduction would equal that on 1 drop daily. Not only did this fail to occur, but, as previously stated, large doses given immediately after the small doses sometimes caused no further reduction in basal metabolism. It was chiefly for this reason that 17 per cent of our house patients (including all four series) showed no reduction in basal metabolism on any dose of iodine. This is about twice as great as the percentage of cases that show no response during the initial administration of large doses. The $\frac{1}{4}$ drop series was responsible for four of the nine failures. In this series only 71 per cent of the cases responded even to large doses. Why the temporary administration of $\frac{1}{2}$, $\frac{1}{4}$ or $\frac{1}{5}$ drop daily, even if not effective itself, should sometimes interfere with the effect of large doses given immediately afterward, is not clear. It is possible that the small doses in some way allow the gland to adjust itself to the effect of iodine before the large doses are given. The fact that in three of the cases in the 1 drop series and in two of those in the $\frac{1}{2}$ drop series, the basal metabolism started to rise a little after showing its maximum drop and that this slight rise continued after large doses were given, thus takes on added significance. The observation that small doses sometimes interfere with the effect of large doses is of interest in connection with the impression of several observers that iodized salt aggravates the disease.¹⁸ From the foregoing considerations it would appear that the real test of whether the reduction of the basal metabolism on 1 drop of compound solution of iodine daily is maximum, is a comparison of its effect with that of larger doses given in other groups of patients, and not with that of larger doses given immediately afterward. This has a general application to all data on iodine. The effects of various doses can be compared only by giving each dose to untreated patients with the disease under the same conditions.

18. Hartsock, C. L.: Iodized Salt in the Prevention of Goiter: Is It a Safe Measure for General Use? *J. A. M. A.* **86**:1334 (May 1) 1926. Hutton, J. H.: Dangers of Iodine in Treatment of Goiter, *Illinois M. J.* **50**:408, 1926. Holmes, M. E.: The Value and Danger of Iodine in Thyroid Disease, *New York State J. Med.* **27**:538, 1927.

From the standpoint of patients with exophthalmic goiter, the results indicate that the indiscriminate use of iodine in any form in the treatment of goiter is probably harmful.

Most of our patients lived within 100 miles of Boston. At present, therefore, our results can be said to apply only to patients in this locality. Many observers are of the opinion that the disease is more intense in goitrous regions (notably in the Great Lakes region) than here. This impression has not yet been corroborated by well controlled data. If it is correct, it also may be true that the minimum dose of iodine necessary to produce a maximum effect is greater in goitrous regions.

SUMMARY

During the daily administration of $\frac{1}{4}$ drop of compound solution of iodine to fourteen unselected hospital patients with exophthalmic goiter, seven showed a reduction in basal metabolism of from 10 to 26 points, six showed no significant change and one showed an increase. During the administration of $\frac{1}{2}$ drop daily to two hospital patients with the disease, one showed a reduction of 14 points and the other showed no change.

In the $\frac{1}{4}$ drop series, the basal metabolism was only slightly lower, and in the two hospital patients who received $\frac{1}{2}$ drop, no lower during the subsequent administration of 30 drops a day, than during the administration of the small doses.

Whereas only 50 per cent of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of $\frac{1}{4}$ drop, 65 per cent showed a reduction during the daily administration of $\frac{1}{2}$ drop, and 88 per cent during the daily administration of 1 drop.

The administration of $\frac{1}{4}$ drop a day caused an average reduction in basal metabolism of only 9 points (from plus 43 to plus 34 per cent) as compared with 14 points (from plus 40 to plus 26 per cent) for $\frac{1}{2}$ drop and 27 points (from plus 36 to plus 19 per cent) for 1 drop.

In the seven patients who responded to $\frac{1}{4}$ drop, the maximum reduction in basal metabolism occurred on the average in five days. In one patient it had started within twenty-four hours.

In a series of outpatients, most of whom had the disease in a mild form, the daily administration of $\frac{1}{2}$ drop produced an average reduction in basal metabolism of only 8 points (from plus 32 to plus 24 per cent) as compared with 21 points (plus 32 to plus 11 per cent) for 1 drop. Large doses given immediately after $\frac{1}{2}$ drop caused a lowering of the metabolism to nearly the same level as 1 drop given initially in the second series.

CONCLUSIONS

The effect of iodine in exophthalmic goiter is not of the all-or-none type, but it is related within certain limits to the size of the dose.

In most of the cases in this hospital, the minimum dose that will produce a maximum reduction in basal metabolism is about 6 mg. of iodine per day. In about 50 per cent of the cases the smallest dose that will produce any effect is greater than 1.5 mg. per day. In 50 per cent of the cases it is 1.5 mg. per day or less.

It would appear that in exophthalmic goiter, iodine must be supplied to the thyroid gland faster than it can be utilized in the elaboration of thyroxin, in order to cause the functional change that is associated with the storage of colloid, and a decrease in the output of thyroxin.

The onset of a reduction in basal metabolism within twenty-four hours after the administration of as little as from 1.5 to 6 mg. of iodine in ten cases, suggests that the output of the thyroid sometimes may be diminished before sufficient colloid can be stored to cause a blocking of the secretion.

In three of the cases observed, the reaction to iodine appeared to be reversible, the administration of $\frac{1}{4}$ to $\frac{1}{2}$ a drop of compound solution daily being associated with an increase in the basal metabolism and in the severity of the disease, and the immediate subsequent administration of large doses being associated with a decrease in both factors.

Doses as small as $\frac{1}{4}$ and $\frac{1}{2}$ drop of compound solution of iodine a day, even when they are too small to cause a reduction in basal metabolism, may sometimes interfere with the effect of much larger doses given immediately afterward. In mild cases of the disease, this phenomenon does not seem to occur.

A comparison of the effects of various doses of iodine, therefore, can be made only by giving each dose to untreated patients with the disease. It is also essential to secure a resting level of basal metabolism before iodine is started.

In the routine preoperative treatment of exophthalmic goiter it is desirable to give suddenly an adequate excess of iodine and not to precede this with small doses.

THE RESPONSE OF THE RETICULOCYTES IN SECONDARY ANEMIAS FOLLOWING VARIOUS FORMS OF TREATMENT *

C. S. YANG, M.D.

AND

CHESTER S. KEEFER, M.D.

PEIPING, CHINA

In recent years, the reticulated erythrocytes in the circulating blood have attracted considerable attention in the study of various anemias. This has been particularly true since Minot and Murphy¹ pointed out that when patients with pernicious anemia were fed large amounts of liver there was a rapid increase in the production of hemoglobin, erythrocytes and reticulocytes. The increase in the reticulated red blood cells was taken as evidence of the efficiency of liver treatment, and their appearance in the circulating blood as an indication of an active production of red blood cells. During the past year, we have been interested in the reticulocyte response in the various forms of secondary anemia, following different kinds of treatment, and in this essay we propose to present the results of a study of fifty-three cases.

LITERATURE

Before presenting the details of our studies, we shall summarize rather briefly the present knowledge regarding these cells. We shall make no attempt to review the enormous literature on this subject since there have been several recent summaries. The essay of Seyfarth² may be consulted for details and an excellent bibliography.

It is generally accepted that the reticulocytes are young and immature red blood cells. Their presence in the circulating blood in numbers above 1 per cent of the total erythrocytes is considered an increase above normal and an indication of increased activity on the part of the bone-marrow. The nature of the reticulum is unknown, but the consensus seems to be that it is derived from the protoplasm of the cell rather than from the nucleus. This has been emphasized recently by Seyfarth,² Cooke³ and others. Cooke³ is of the opinion that the

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* From the Department of Medicine, Peiping Union Medical College.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**:470 (Aug. 14) 1926; A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. A. M. A.* **89**:759 (Sept. 3) 1927.

2. Seyfarth, Caryl: Experimentelle und klinische untersuchungen über die vitalfärbbaren Erythrozyten, *Folia haemat.* **34**:7, 1927.

3. Cooke, W. E.: The Artificial Production of Punctate Basophilia and Reticulation in Erythrocytes, *Am. J. M. Sc.* **177**:537, 1929.

reticulum is probably a hemoglobin compound and qualitatively the same as basophilic stippling and polychromasia.

Reticulocytes in the Normal Circulating Blood.—In adults, the number of vitally stained cells in the circulating blood varies from 0.2 per cent to 1 per cent. Seyfarth and Jurgens⁴ showed that in normal infants at birth the reticulocytes number approximately 7 per cent. Following birth, the number decreases rapidly, so that by the sixth week the average count is only 0.7 per cent. In premature infants at birth, the reticulocytes are between 10 and 30 per cent, and the percentage decreases more slowly than in normal infants. Following the sixth week of extra-uterine life, the reticulocytes are not increased above 1 per cent, except under certain physiologic or pathologic circumstances.

Different animals vary in the number of reticulocytes they have normally. Seyfarth² stated that the normal count for horses, sheep, hogs, cats and cows is between 0.1 and 0.2 per cent, and for dogs between 0.2 and 0.5 per cent. Smaller animals have higher counts. Guinea-pigs have between 0.5 and 5 per cent; rats, from 3 to 5 per cent; mice, from 4 to 6 per cent, and rabbits from 3 to 8 per cent. Young animals have more reticulocytes than old ones. It is also known that the number of reticulocytes in animal embryos may be high. In mice embryos, they vary between 30 and 40 per cent. Seyfarth and Jurgens⁴ were able to show that at some time during embryonic life, all the red cells had reticulum. This observation, together with the fact that there was an abundant reticulum in many cells with a perfectly normal nucleus, led them to the conclusion that the reticulum was a part of the protoplasm and was not derived from the nucleus. Furthermore, reticulum was present in every cell containing hemoglobin at some time during its development. This view was supported by the work of Cooke,³ who was able to produce reticulation artificially in any red cell without a nucleus. He expressed the opinion that the reticulum was probably a hemoglobin compound which was able to take up the stain because of an alteration in the red cell membrane.

Vitally stained red cells have been described as occurring in various numbers in different diseases in which the hematopoietic system is involved. These conditions may be reviewed as follows:

Reticulocytes in Pathologic States.—The percentage of reticulocytes may be markedly increased in malaria, hemolytic jaundice, post-hemorrhagic anemias and anoxemia, and following the intravenous injection of distilled water into animals and following chemical intoxi-

4. Seyfarth, Caryl and Jurgens, R.: Untersuchungen über das Verhalten der vitalgranulierten roten Blutzellen (Reticulocyten) bei Embryonen und Neugeborenen, Virchows Arch. f. path. Anat. 266:676, 1927-1928.

cation such as phenylhydrazine poisoning. There may be a slight increase in their percentage in leukemia, Hodgkin's disease, carcinomatosis of the bone-marrow, kala-azar and chlorosis. In other conditions, such as aplastic anemia, the count is constantly low.

During recovery from various anemias, the percentage of reticulocytes may increase spontaneously. This is true during spontaneous recovery in acute posthemorrhagic anemias, pernicious anemia, malaria and the anemias following blood destruction, of which phenylhydrazine intoxication is an example.

The percentage of reticulocytes is also increased in some anemias, following various forms of treatment: following transfusion in pernicious anemia⁵ and posthemorrhagic anemia; following splenectomy in splenic anemia⁶ and pernicious anemia;⁵ following ergosterol in the anemia of dogs after bile fistulas;⁷ following cod-liver oil and high caloric diet in the anemia associated with dysentery;⁸ following high liver feeding in pernicious anemia,¹ sprue,⁹ anemia due to tapeworm,¹⁰ anemia due to hookworm,¹¹ the anemias of pregnancy,¹² and the anemias of undernutrition,^{11 12} and of carcinoma of the stomach;¹³ following iron in splenic anemia, chlorosis and the anemia of dysentery¹¹; following liver extract in pernicious anemia,¹⁴ sprue,^{15 16 17} the anemia due

5. Minot, G. R., and Lee, R.: Treatment of Pernicious Anemia, Especially by Transfusion and Splenectomy, Boston M. & S. J. **177**:761, 1917.

6. Dameshek, W.: The Reticulated Red Cells, Their Clinical Significance: Boston M. & S. J. **194**:759 (April 29) 1926.

7. Seyderhelm, R., and Tammann, T.: Die Bedeutung der Galle für die Blutmauserung, Klin. Wchnschr. **6**:1177 (June 18) 1927.

8. Berglund, H.; Keefer, C. S., and Yang, C. S.: Deficiency Anemia in Chinese, Responding to Cod Liver Oil, Proc. Soc. Exper. Biol. & Med. **26**:418, 1929.

9. Bloomfield, A. L., and Wyckoff, H. A.: Remission in Sprue Following High Liver Diet: Case Report, California & West. Med. **27**:659, 1927.

10. Isaacs, R.; Sturges, C. C., and Smith, M.: Tapeworm Anemia, Arch. Int. Med. **42**:313 (Sept.) 1928.

11. Keefer, C. S., and Yang, C. S.: The Value of Liver and Iron in the Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929.

12. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy: Particularly in Pernicious Anemia, Am. J. M. Sc. **175**:581, 1928.

13. Heath, E. H.: Personal communication to the authors.

14. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Larson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects Upon the Production of Immature and Mature Red Blood Cells, Am. J. M. Sc. **175**:599, 1928.

15. Bloomfield, A. L., and Wyckoff, H. A.: The Treatment of Sprue with Liver Extract (343), Am. J. M. Sc. **177**:209, 1929.

16. Ashford, B. K.: Evaluation of Liver Extract in Treatment of Anemias of Sprue; Preliminary Note, J. A. M. A. **91**:242 (July 28), 1928.

17. Richardson, W., and Klumpp, T. G.: Sprue; Case Treated with Authorized Liver Extract Effective in Pernicious Anemia, New England J. Med. **199**:215 (Aug. 2) 1928.

to tapeworm,¹⁸ and the anemias of childhood;¹⁹ following liver and iron in the anemias of pregnancy, chlorosis, hookworm disease and the anemia of undernutrition.¹¹

It may be seen, therefore, that the percentage of the reticulated red cells may be increased in various forms of secondary anemias and following different kinds of treatment.

OBSERVATIONS IN FIFTY THREE CASES

The reticulocyte counts of the cases reported in this paper have been summarized briefly in table 1. It may be seen that they varied from

TABLE 1.—*Relationship Between Type of Secondary Anemia and Reticulocyte Response*

Type of Anemia	Cases	Reticulocytes, per Cent
Hookworm.....	5	5-14
Pregnancy.....	4	1.4-10
Dysentery (chronic).....	7	1.4-28
Undernutrition.....	5	1.0-15
Chlorosis.....	3	0.2-7
Posthemorrhagic anemia.....	8	1.0-15
Malaria.....	3	8-35
Splenic anemia.....	5	4-8
Anemia following splenectomy.....	2	5-8
Kala-azar.....	6	3-5.6
Postinfectious anemia.....	3	0.4-4.6
Aplastic anemia.....	1	0-1.2
Nephritis.....	1	0-3

TABLE 2.—*Relationship Between Total Number of Erythrocytes and the Reticulocyte Response*

Total Number of Erythrocytes	Percentage of Reticulocytes
1,000,000 to 1,500,000	0-35
1,500,000 to 2,000,000	1-13
2,000,000 to 3,000,000	10 or less
3,000,000 to 4,000,000	10 or less
4,000,000 to 5,000,000	7 or less

1 to 35 per cent. The intensity of the increase depended on the severity and the cause of the anemia, and the form of treatment employed during recovery.

The most marked reactions were seen in the anemias associated with hookworm infection, hemorrhage, dysentery, undernutrition, pregnancy and malaria. In the other forms the count varied.

The relationship between the severity of the anemia and the reticulocyte response is recorded in table 2. As a general rule, the

18. Richter, Oscar; Maurer, S., and Eyl, M.: Treatment of Severe Dicrocoeliosis (Latus Anemia), with a High Caloric Diet, Rich in Liver Extract and Vitamins, J. A. M. A. **91**:1462 (Nov. 10) 1928.

19. Faber, K. F.: Value of Liver Extract (343) in Identifying and in Treating Certain Anemias; Case of Probable Primary Anemia in Infant One and One-Half Months Old, Am. J. Dis. Child. **36**:1121 (Dec.) 1928.

lower the original erythrocyte count, the higher the reticulocyte count may rise during recovery. This was also noted by Minot, Murphy and Stetson¹² following liver therapy in pernicious anemia, and in a few patients with secondary anemia. This reaction varies with the type of anemia and of treatment.

The relationship between the response of the reticulocytes and different forms of therapy in various anemias is summarized in table 3. Besides the fact that the severity and the cause of the anemia influence the reticulocyte response, it seems clear that certain forms of treatment can bring about an increase in the percentage of reticulocytes in some anemias and not in others. For example, the production of reticulocytes in kala-azar does not seem to be influenced by any form of treatment, and the same is true of that in aplastic anemia.

TABLE 3.—*Relationship Between Form of Treatment and Reticulocyte Response*

Type of Anemia	Percentage of Reticulocytes in Spontaneous Recovery	Percentage of Reticulocytes with Various Forms of Treatment				
		Trans-fusion	Iron	Liver	Liver and Iron	Cod Liver Oil
Hookworm.....	4-8	5-10	4-14
Pregnancy.....	1.4-1.6	10	8-10	6-10
Dysentery.....	4	1-2	4-8	12-23
Undernutrition.....	10	15
Malaria.....	8-35
Chlorosis.....	2-7	3	5-6
Posthemorrhagic anemia.....	1-4	2-8	1-3	1-15
Splenic anemia.....	4-8	8	4	4-6
Anemia following splenectomy.....	4-6	8
Kala-azar.....	1-5	1.5	1-5	1-5	1-5	1-5
Postinfectious anemia.....	1-4	1-4	1-4
Aplastic anemia.....	0.5-1	0.5-1	0.5-1	1	1	1
Nephritis.....	3	3

The reticulocyte reactions of the various anemias can be discussed in greater detail.

Anemia Associated with Chronic Dysentery.—In the group presenting anemia with chronic dysentery were eight patients. The reticulocyte counts varied from 1.4 per cent to 28 per cent during the period of recovery. In two patients previously reported by Berglund, Keefer and Yang,⁸ the improvement followed cod liver oil and a general diet. In others, improvement occurred following transfusion or treatment of the dysentery and a high caloric diet. The anemia in these patients seemed to be related to the state of nutrition. When the patients received an adequate diet, the anemia improved.

Anemia of Pregnancy.—Seyfarth² reported that the reticulocytes may be increased over 1 per cent in normal pregnancy. In the anemias of pregnancy, Dameshek⁶ distinguished two types according to the reticulocyte response. In one group, the recovery from anemia was like that in pernicious anemia, that is, with an increase in the production

of reticulocytes. In the other, the recovery was like that in the secondary anemias in which recovery takes place without any increase in the production of reticulocytes. Minot, Murphy and Stetson¹² have recorded an increase in the reticulocyte count in the anemias of pregnancy, following liver feeding. Two of our patients recovered following treatment with liver, and the reticulocyte counts were increased.

Posthemorrhagic Anemia.—The reticulocytes may increase to between 30 and 40 per cent in the circulating blood following an acute hemorrhage. This is true in both man and experimental animals. In the chronic posthemorrhagic anemias, the production of reticulocytes may not be increased, and recovery may take place following transfusion or liver and iron without any increase. On the other hand, there are exceptions in which the reticulocytes do increase to 15 or 17 per cent during recovery in this type of anemia following liver and iron.

Anemias of Undernutrition.—The patients who had anemia associated with undernutrition included those in whom the undernutrition was due to a poor and inadequate diet without any other demonstrable cause. These patients recovered promptly following treatment with liver and iron and the routine hospital diet.

Chlorosis.—The cases of chlorosis studied occurred in women. The anemia was characterized by a normal number or a slightly reduced number of erythrocytes and a greatly reduced hemoglobin content. No definite cause for the anemia could be discovered, but recovery occurred when iron, or liver and iron, were added to the diet. As a rule, the reticulocytes were not increased above 5 to 7 per cent.

Kala-Azar Anemia.—In our experience, the reticulocytes have never been increased above 6 per cent in any patient with kala-azar and anemia. This is true regardless of the severity of the anemia or any form of treatment.

Aplastic Anemia.—In aplastic anemia, the reticulocytes are constantly low. In the cases recorded by Shen,²⁰ Dameshek⁶ and Seyfarth² the counts were never above 4 per cent. In one case the count was never over 1 per cent. This was true regardless of treatment.

Splenic Anemia.—In the group with splenic anemia, we have included the patients with splenomegaly and anemia of unknown cause. We studied three patients before splenectomy and two patients who had become anemic one and five years respectively, following splenectomy. The reticulocytes varied between 4 and 8 per cent in each group. In one patient, iron was effective in producing rapid improvement with an increased reticulocyte count.

20. Shen, Dorothy: Aplastic Anemias in North China, Nat. M. J. China **14**: 389 (Dec.) 1928.

Anemia of Malaria.—The percentage of reticulocytes may be greatly increased in malaria, as shown by Yang and Berglund,²¹ Seyfarth,² Davidson and McCrie²² and others. In the cases we have observed, the counts varied from 8 to 35 per cent prior to specific treatment with quinine.

Postinfectious Anemia.—The recovery of patients from anemia following infections, such as typhus and relapsing fever, was not associated with an increase in the production of reticulocytes. The count varied from 0.4 to 4.6 per cent.

COMMENT

In a previous paper,¹¹ we pointed out that when both liver and iron were given to some patients with secondary anemia, the regeneration of hemoglobin could be accelerated. This was striking in the anemia associated with hookworm infection, but it was also noted in other forms of secondary anemia. In some instances, the recovery from the anemia occurred in the same way as that from pernicious anemia following liver diet, namely, with an increased number of reticulocytes in the circulating blood. In others, recovery was not accompanied by an increase in number of reticulocytes.

We wish to emphasize the fact that in the case of a number of secondary anemias, patients may recover following treatment with liver and iron, or other forms of therapy and during the period of recovery may show an increase in the percentage of reticulocytes. The intensity of the reaction depends not only on the type of treatment but on the cause and the severity of the anemia. In some cases, the reticulocytes were never increased above 5 per cent regardless of the form of therapy or the severity of the anemia. This was particularly true of the anemia of kala-azar, the postinfection anemias, the aplastic anemias, and of most of the chronic posthemorrhagic anemias. In malaria, the percentage of reticulocytes was generally increased regardless of treatment.

The most striking responses following the various forms of treatment mentioned, were seen in the anemias of hookworm infection, undernutrition, pregnancy and dysentery. In all of these anemias, poor nutrition seemed to play a considerable part. A proper diet supplemented with liver and iron or, in some instances, with cod liver oil, was capable of bringing about an increase in the percentage of reticulocytes and an improvement of the anemia.

21. Yang, C. S., and Berglund, H.: Difference in Reticulocyte Behavior in Anemia from Malaria and in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **26**:417, 1929.

22. Davidson, L. S. P., and McCrie, J. G.: The Phenomenon of Reticulation and Alteration in Size of Red Blood Corpuscle After Liver Therapy, *Lancet* **2**:1014 (Nov. 17) 1928.

Minot, Murphy and Stetson ¹² have recorded a similar reaction following liver diet in some secondary anemias. Two of their cases were associated with pregnancy and the other three with disturbances in nutrition. Bloomfield and Wyckoff ⁹ have reported favorable results following liver feeding in anemia associated with sprue, and Isaacs, Sturges and Smith ¹⁰ and Richter, Maurer and Eyl ¹⁸ have recorded the same for anemia due to broad tapeworm.

It would appear from the cases of secondary anemia on which this study is based and the cases previously reported by others that many forms of secondary anemia react in the same way following treatment with liver, or liver and iron, as pernicious anemia reacts following treatment with liver or liver extract. The exact explanation for these observations awaits further study.

SUMMARY AND CONCLUSIONS

In this study of fifty-three cases of secondary anemia, we were able to show that the response of the reticulocytes depends on the severity and the cause of the anemia, and the form of treatment employed during recovery. The highest reticulocyte counts were observed in malaria, anemia due to hookworm, and the anemias associated with dysentery, undernutrition and pregnancy. In the latter four conditions, nutritional disturbances seemed to play a part in the production of anemia, and when the patients with these conditions were treated with liver or liver and iron or cod-liver oil and a high caloric diet, the anemia decreased and the percentage of reticulocytes increased.

In many of the cases of secondary anemia, the results produced in the reticulocyte count by the forms of treatment mentioned were as striking as those seen in pernicious anemia following treatment with liver or liver extract. It would appear, therefore, that feeding of liver as a method of treatment in anemia is not specific for pernicious anemia, but has a beneficial effect in many forms of secondary anemia. In many instances, liver and iron together were more effective than liver or iron alone.

THE ETIOLOGY OF EMPHYSEMA *

L. M. LOEB, M.D.

CHICAGO

According to Fraenkel,¹ emphysema is found in more than 5 per cent of all autopsies. It is rarely found in children, but increases in frequency with each decade. It is often present in persons about 40 years of age, and frequently occurs during old age. Generally it is described as occurring in three types (excluding interstitial emphysema, which has no relation to the disease under discussion) namely: compensatory, atrophic and hypertrophic or vesicular emphysema.

TYPES OF EMPHYSEMA

Compensatory.—Compensatory emphysema is a condition in which one portion of the lung increases in size and function, when another portion is destroyed or temporarily useless. It occurs, for instance, in association with pneumonias, pleural effusions and pneumothorax. Anatomically, there is found an enlargement of the normal lung; there are no variations from the normal structure; the unaffected lung, as a result of distention, has an increased vital capacity and is able to perform a greater amount of work than when in its usual condition. The tissues show no similarity to those truly emphysematous. This change is in no way related to true emphysema and the term should not be used, as it creates great confusion in the literature. Its use is no more justified than that of speaking of the compensatory enlargement of a kidney, when the opposite kidney has been removed, as of a compensatory nephritis. True emphysema can never compensate for diseased lung tissue, because the emphysematous lung is totally or almost totally functionless.

Atrophic.—The term atrophic emphysema is usually applied to the type of emphysema most commonly found in senility. It is said to be “a part of the atrophic change that occurs everywhere in the body with advancing years. The alveolar walls become atrophic and the lungs lose their elasticity. In contrast to true emphysema, the lungs are small and retracted.”² Although this statement is found universally in the

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* From the Physiology Laboratory of the University of Chicago and Cook County Hospital.

1. Fraenkel, quoted by Staehelin: *Handbuch der inneren Medizin*, 1914, p. 662. This article and one by the same author in *Ergebn. d. inn. Med. u. Kinderh.*, 1915, p. 516, contain a complete bibliography on emphysema.

2. Hamman, L.: *Oxford Medicine*, New York, Oxford University Press, 1918, vol. 2, p. 61.

literature, there is no evidence for its truth. The condition does not differ from hypertrophic or vesicular emphysema except in the size of the lungs. This difference may reasonably be attributed to the diminution of function in senility. The size of the lung, like that of every other organ, is known to vary with its use. The lungs of athletes, of users of wind instruments, of glass blowers and even of persons who are dyspneic for reasons fundamentally nonpulmonary are known to be larger than those of persons of sedentary habits or not subject to similar functional disturbances. In senile persons, who are inactive, atrophy of disuse occurs, and even the added emphysematous process may not bring the lungs to a normal size. I see no reason for assuming that the etiologic basis of atrophic emphysema differs from that of the hypertrophic type. Normally, the amount of lung tissue is much greater than is essential for life without marked physical activity. Usually, if lung tissue is destroyed, the remaining lung enlarges. But if normal activity is not resumed, a return to the normal size need not occur. Thus it was possible to remove three lobes of a dog's lung by successive lobectomies without producing dyspnea while the dog remained relatively inactive. Autopsy several weeks after operation presented no compensatory enlargement; the total volume of lung tissue was not much more than half of the normal. Similar conditions might well account for the absence of hypertrophy in association with the emphysema of senility.

Hypertrophic or Vesicular.—In this type of emphysema the lungs are enlarged as a result of an enormous increase in the size of the air vesicles, particularly at the apexes and anterior margins of the lungs. The air spaces may be as large as a hen's egg. They are produced by rupture of the intra-alveolar septums and the merging of many alveoli. It is inconceivable that such spaces can carry on any of the respiratory functions. The capillaries are destroyed, and the passage of air to and from these spaces would be mechanically difficult. Several facts appear to prove that, in at least many cases, these bullae do not communicate with the bronchioles.

Boenninger³ stated that a pressure of 300 mm. of mercury was insufficient to diminish materially the size of some of these air pockets.

Analysis of the contents of the vesicles proved them to be composed chiefly of nitrogen, the oxygen having been taken from the air originally occupying them (Benecke⁴).

Except for the tissue grossly involved, the structure of the lung appears intact unless other concomitant disease processes are present.

3. Boenninger: *Verhandl. d. Kong. f. inn. Med.*, 26th Congress, Wiesbaden, 1909.

4. Benecke: *Verhandl. d. deutsch. path. Gesellsch.*, 1913, p. 448.

Some have reported the elastic tissue in the alveolar walls as diminished, others as increased. The estimation of the normal amount is so difficult, however, that it is impossible to draw any conclusions from these reports. The tissue involved is naturally inelastic.

Many theories as to the causation of emphysema have been put forth. Some of these appear to be without any foundation. It has been suggested that emphysema is due to a congenital deficiency of the elastic tissue. The only basis for this hypothesis is that the disease has been found in several members of a family. The fundamental defect is believed by some to be an abnormal condition of the wall of the chest.⁵ Thus high grades of emphysema have been present in cases of marked kyphosis and scoliosis, and the "barrel chest" of emphysema has been accused of being the cause and not the effect of the pulmonary change. The frequency of emphysema with or without defects in the wall of the chest makes it appear probable that their association is accidental.

In the old textbooks, prolonged or frequently repeated expiratory effort was emphasized as a cause. Glassblowers, blowers of wind instruments, etc., were thought to be commonly affected by emphysema. Both clinical and pathologic evidence have served to discount this factor in the etiology. It has been definitely proved that such effort results in enlargement of the lung, but there is no basis for the further assumption that "if the increased (intra-alveolar) pressure is maintained for a long time, the lung loses its resiliency and a condition in all respects similar to true emphysema occurs."² It is also frequently stated that persistent so-called compensatory emphysema changes to the vesicular form. There is no clinical or experimental proof for this belief. Kuhn⁶ attempted to produce pulmonary enlargement in dogs by applying masks over their heads. These masks had valves increasing the resistance to expiration. Photographs of his dogs prove an enlargement of the chest, but even after the resistance had been continued for more than a year, apparently nothing suggestive of true emphysema developed in the lungs.

The most generally accepted and most plausible theory as to the pathogenesis of emphysema is that of mechanical obstruction to the air current. From the physical standpoint this would be most likely to result in increased expiratory effort, no matter what might be the nature or the location of the obstructing element. Increased difficulty in inspiration, unless of high grade, is easily overcome by a commensurate increase in the activity of the muscles of the wall of the chest and diaphragm; expiration, on the other hand, being normally a passive

5. Freund, W. A.: *Ueber primäre Thoraxanomalien*, Berlin, 1906.

6. Kuhn: *Die Anwendung der Lungensaugmaske*, *Therap. Monatschr.*, 1910, p. 411.

process with relaxation of the musculature, offers greater difficulties. Moreover, the air passages open during inspiration and collapse during expiration, so that any stenosis is exaggerated during the latter.

One might conceive of the effect of an obstruction in the air passages as analogous to that of an enlarged prostate on the bladder. A gradual increase in the residual air in the parts distal to the obstruction might occur, resulting in dilatation of the alveolar spaces. There is little doubt that this actually takes place, but there is no certainty that a true emphysema results. The effect would simulate that of spasmodic expiratory effort, except for its greater intensity and continuity.

If obstruction causes emphysema, the end-result should be the same, no matter what the position of the obstruction. The following are instances of clinical types in which emphysema apparently resulted from obstruction at various levels.

Nasal Obstruction: A man presented himself, complaining of severe dyspnea on slight exertion. On examination, the heart and lungs seemed normal except that the lung volume appeared increased. Roentgen examination gave negative results. The nasal passages were almost completely blocked by polyps. This man was not conscious of the occlusion, was not a mouthbreather even at night and was compelled to increase his respiratory effort to overcome the obstruction. Removal of the polyps resulted in marked diminution of dyspnea and reduction in the size of the lungs.

Laryngeal Obstruction: A young man with cardiac irregularity and physical characteristics of high-grade emphysema was found to have a paralysis of the left vocal cord.

The most extensive emphysema that I have seen occurred in a man whose vocal cords had become agglutinated as a result of tuberculosis to such an extent that only a buttonhole slit remained. The pulmonary tuberculosis was insignificant.

Tracheal Obstruction: A woman, aged 70, with dyspnea, cyanosis and pulmonary enlargement had a large goiter which produced displacement and kinking of the trachea.

At lower levels emphysema is found frequently in cases in which foreign bodies and tumors involve or press on the bronchi.

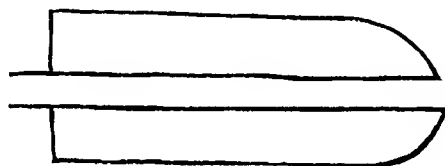
Instances of the types noted lend force to the theory that obstruction of the air passages may produce emphysema. A total occlusion, of course, could not cause distention of the alveoli, but rather an atelectasis. In spite of numerous statements in the literature to the contrary, little experimental work has been done to prove or disprove this theory. Except for the work of Kuhn, I know of none which has any bearing on this problem. Because of the therapeutic possibilities due to the recent great advances in bronchoscopy, it is important to determine the facts of the case. If emphysema is produced by obstruction in the larger air passages, operative removal of the noxious agent would be of prime value in its prevention and treatment. The early recognition should serve to obviate the more advanced forms and, with them, the damage to the circulatory system.

EXPERIMENTAL WORK

Numerous methods were used in attempting to produce obstruction at various levels of the respiratory tracts of dogs. Many technical difficulties were encountered, and the failures are reported for the sake of others engaged in like work.

Narrowing of a Main Bronchus by Ligature or Metal Clamps.—The former invariably resulted fatally, usually after three or four days, either by hemorrhage (cutting through the bronchial artery) or by pneumothorax and pleural infection (cutting through the bronchial wall). When metal clamps were used, the stenosis was only temporary; within a week the clamps could be seen by bronchoscope to lie within the bronchus and the bronchus had resumed its normal contour.

Narrowing of the Trachea by Ligature or by Broad Tape.—No matter what material was used, the result was the same. Within a week, the external pressure had produced atrophy of the tracheal wall and a fistula appeared, which vitiated the experiment.



Brass tubes used in permanent partial tracheal obstruction.

Narrowing of the Larynx by Actual Caution of the Vocal Cords.—Frequent attempts proved entirely futile. Within a week all of the animals, that survived, had recovered sufficiently to manifest normal functioning of the vocal cords. In none did these present agglutination.

Many efforts were made to produce partial obstruction of the trachea and bronchi by the introduction of foreign bodies of various types into their lumina. Melted paraffin and large molds of paraffin (melting point 50 C.) forced into the bronchi and trachea by way of a bronchoscope were ineffective because they were ejected by the dogs within a few days. Metal cups were also made, perforated at the bottom so as to permit the passage of some air. These could be kept in place only by forcing them into the bronchi as far as possible and attaching to them fine wires, which entered the bronchial mucosa. The openings in these cups, however, soon became closed by mucus, and the obstruction was complete.

A technic for permanent partial tracheal obstruction was finally devised which proved entirely successful. Brass tubes were made as illustrated in the accompanying figure. The diameter of the outer tubes was 18 mm., as nearly as possible equal to the diameter of the trachea of a dog weighing 15 kilograms. The diameter of the inner tubes was

from 4 to 5 mm. so that the area of the duct was less than one-fifteenth of that of the trachea. These tubes were introduced into the trachea by tracheotomy, the curved end toward the body. On account of their size, it was not possible for them to pass through the larynx. The trachea was not sewed, but the fascia and skin were closed loosely, so that any air escaping from the trachea could leave the body instead of being forced into the subcutaneous spaces.

The immediate results of operation were as follows: about two-thirds of the dogs died within twenty-four hours. The cause of death appeared to be a displacement of the tubes upward by coughing; pressure against the vocal cords produced intense tachypnea and death. When tachypnea occurred during periods of observation, the lives of the dogs could be saved by removal of the plugs. In these cases the tubes were too small to fit snugly into the trachea and to be held in situ. Eight dogs survived. Most of these presented an extensive subcutaneous empysema within twenty-four hours, in some instances doubling their original size. This did not appear to incommode them or to affect their health in spite of its grotesqueness. The air, if great in amount, was removed partially by puncturing the back by a trocar. When not so removed, it disappeared spontaneously in from one to two weeks. Cardiac irregularity was noted in each case after the operation; in most instances it disappeared within a few days. In two dogs it persisted for several months. Electrocardiogram of one dog were interpreted as showing sinus arrhythmia, probably due to vagus irritation.

The dogs were examined at least once a week during the period of their survival. The examinations included measurements of the chest, percussion, auscultation and fluoroscopy with and without the use of iodized poppy seed oil—40 per cent. Most of the dogs remained aphonic, but some were able to bark loudly within a few weeks. On exertion, such as running up a flight of stairs, all presented severe dyspnea and became exhausted; some also vomited. While at rest, they appeared normal except that during one hot period, two dogs (the only ones successfully operated at that time) suffered intensely. They became prostrated, had hyperpyrexia (up to 106 F.) and it was felt that they survived only because of frequent bathing. No definite changes were discovered by measurements, percussion or auscultation. Fluoroscopy showed the diaphragm to be somewhat lowered, as indicated by a clear space between the heart shadow and the dome of the diaphragm.

The dogs were killed at intervals of approximately two months. The longest period of observation was fourteen months. Only one died spontaneously. The first dog was killed by a blow on the head by a heavy hammer, the others by bleeding under anesthesia. The former

method was abandoned, because it was found that the lungs contained too much blood for satisfactory sections. During bleeding, tracheotomy was performed, the plug removed and during the last gasps of the dog a diluted solution of formaldehyde, U. S. P. (1:10) was permitted to flow into the trachea from a height not exceeding 50 cm. Artificial respiration was carried on, and the dog was turned in various positions so that the fixative solution might reach all parts of the lungs. A diluted solution of formaldehyde (1:10) was also injected into the abdominal cavity to prevent decomposition. The organs were left to harden in situ for forty-eight hours before dissection; the lungs were then removed and placed in a diluted solution of formaldehyde (1:10) for a week before sectioning.

At autopsy in all cases hypertrophy and dilatation of the right ventricle were present. The trachea at the site of the plug showed atrophy of the cartilage and thickening of the mucosa. Microscopically, there was metaplasia of the mucous membrane. The lining epithelium was squamous in type and consisted of seven or eight layers. On gross examination, the lungs showed no semblance to the vesicular emphysema of the human being. Enlarged alveoli were sometimes seen at the apical margins and in a small lobe lying behind the heart; these were particularly noticeable when examined under low magnification. Microscopically, a few of the alveoli and infundibula in the areas noted appeared dilated, and in a few places the alveolar walls seemed ruptured. These changes were so few and insignificant that one could not feel certain of any pathologic observations in spite of careful study of many sections.

In dogs in which bronchial obstruction had been produced by the introduction of plugs of similar construction, but of smaller caliber, partial obstruction was not obtained because of complete closure of the orifice by mucus.

COMMENT

As a result of these experiments, it appears evident that partial obstruction to respiration alone in dogs is insufficient to produce a condition similar to the vesicular emphysema of man. It is also improbable that emphysema in man can be due to obstruction alone. In spite of the negative results obtained, there is a great amount of clinical evidence pointing to obstruction as an important factor in the pathogenesis of emphysema. It appears, however, that, if so, a concomitant alteration of the finer air passages is essential. Such an alteration occurs in whooping cough and chronic bronchitis, which present both infection and obstruction. In the few areas noted, in which microscopically a picture resembling that of vesicular emphysema was observed, the lining cells of the alveoli were absent and the elastic tissue entirely

denuded. Such a condition would serve to weaken the alveolar walls and result in their destruction.

Further attempts were made to test the validity of this assumption. Irritants of several types were introduced into the lungs via the bronchoscope, simultaneously to produce obstruction and inflammation. Among others, powdered talcum, barium and bismuth salts and iron powder were used. Unfortunately, even the heavy powders were expelled rapidly, judging by fluoroscopy, within a few hours. The dog reacts unfavorably to pulmonary infections, and the addition of this factor to obstruction does not promise satisfactory experimental results.

Many bronchoscopists have reported the existence of bronchiectasis in cases of partial obstruction of a bronchus by a foreign body with infection of the bronchus below.⁷ A similar association in the bronchioles and infundibula might well be responsible for dilatation of the finer air spaces. It is true that at autopsy emphysema may be found without concurrent infection. This does not prove, however, that an infection was not present when the emphysema developed. If, as is generally believed, whooping cough gives rise to emphysema, the latter would persist after the infection of the bronchioles had disappeared. Similarly, other infections might be overcome, but there is no possibility of a *restitutio ad integrum* following emphysema. The fact that emphysema is frequently a terminated process and not progressive in character is indicated by the fact that in the vast majority of cases found at autopsy the disease has been entirely unsuspected, and not even careful scrutiny of the history presents symptoms suggestive of emphysema.

CONCLUSIONS

1. Long continued high-grade obstruction of the air passages of dogs was insufficient to produce a pathologic picture simulating vesicular emphysema in man.

2. If obstruction is a factor, an additional factor or factors, as an associated infection of the finer respiratory passages is an essential concomitant. It is possible, but improbable that an expiratory obstruction much greater than inspiratory might be adequate.

NOTE.—While this paper was in press, my attention was called to an article by W. H. Harris and F. P. Chillingworth (*The Experimental Production in Dogs of Emphysema with Associated Asthmatic Syndrome by Means of an Intratracheal Valve*, *J. Exper. Med.* **30**:75, 1919). The technic employed was almost identical with that described. The presence of a gutta percha ball acting as a valve to increase the expiratory difficulty should make little change in the resulting pathologic condition. Their dogs were kept for periods of from one day to three weeks. In some of these animals (number not stated) infection played a

7. Many papers from the Clinic of Chevalier Jackson. Myerson, M. C.: *Benign Neoplasms of Bronchus*, *Am. J. M. Sc.* **176**:720, 1928.

rôle as evidenced by the presence of lobular pneumonia. Their conclusions were that the production of emphysema was found to vary in extent and degree according to the type of valve employed and the duration of the experiment. My first impression also was that I had succeeded in producing emphysema, but I discovered that there were no greater changes after fourteen months than in the shorter experiments. They also stated that in control animals and "in a considerable proportion of dogs employed in routine physiological laboratory work" slight emphysema was noted on the edges of the lung. In all dogs examined, operated and control, the alveoli and infundibula at the margin were much larger than those found elsewhere, and they were therefore considered as normal, not emphysematous. The photomicrographs and photographs of the gross lung illustrating their article were practically identical with my observations, but I did not interpret these changes (the pneumonia excepted) as pathologic, and several pathologists who were consulted did not believe them to be emphysematous. In brief, their technic and results were practically identical with mine, but the conclusion that tracheal obstruction (without infection) resulted in emphysema does not agree with that reached by me.

AMYLASE IN THE BLOOD IN SUBACUTE AND IN CHRONIC PANCREATIC DISEASES *

E. G. WAKEFIELD, M.D.

Fellow in Medicine

J. M. McCAUGHAN, M.D.

Fellow in Surgery, the Mayo Foundation

AND

CHARLES S. McVICAR, M.D.

ROCHESTER, MINN.

Since 1833, when Payen and Persoz ¹ precipitated a starch-splitting substance from malt and gave it the name of diastase, the so-called diastatic activity of blood and of the various excreta from man and animals has been widely studied in health and in disease. The diastatic activity of the blood was observed first by Magendie ² who showed that the blood was capable of splitting starch into sugars. In general, not much advancement was made, in spite of the methods offered from time to time, until Wohlgemuth ³ described a quantitative method for determinations of amylase in 1908. Following Wohlgemuth's work, various quantitative methods were described which depended on the ability of amylase to effect a given change in a known solution of starch. Results obtained by these methods led such authorities as Van Slyke and Cullen ⁴ to think that, in general, enzymes obey the law of mass action and that apparent divergences from this law are due to secondary reactions. It has been objected that enzymes do not obey the law of mass action because they are colloidal solutions. There is evidence, however, to show that this may not be so. Northrop, ⁵ for instance, contended that it is reasonable to assume that colloidal solutions are governed by the law of mass action because it can be shown that colloidal solutions obey the law of gases and the laws of thermodynamics from

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* From the Division of Medicine, the Mayo Clinic.

1. Payen and Persoz: *Mémoire sur la diastase, les principaux produits de ses réactions et leurs applications aux arts industriels*, Ann. chim. & phys. **53**:73, 1833.

2. Magendie: *Note sur la présence normale du sucre dans le sang*, Gaz. méd. de Par. **1**:734, 1846.

3. Wohlgemuth, J.: *Ueber eine neue Methode zur Quantitativen Bestimmung des diastatischen Ferments*, Biochem. Ztschr. **9**:1, 1908.

4. Van Slyke, D. D., and Cullen, G. E.: *The Mode of Action of Urease and of Enzymes in General*, J. Biol. Chem. **19**:141, 1914; **28**:391, 1916-1917.

5. Northrop, J. H.: I. *The Inactivation of Trypsin*, J. Gen. Physiol. **4**:227 (Jan.) 1921-1922. II. *The Equilibrium Between Trypsin and the Inhibiting Substance Formed by Its Action on Proteins*, J. Gen. Physiol. **4**:245 (Jan.) 1921-1922.

which the law of mass action may be derived. Furthermore, Northrop has confirmed his contention by experimental observation.

Northrop and Hussey⁶ conceived the idea of measuring the viscosity of solutions containing enzymes during the period of action of the enzymes. This they did by using a 3 per cent solution of gelatin during tryptic digestion. They found that the time required to effect a given change in the initial viscosity of the substrate was inversely proportional to the amount of the enzyme employed (Arrhenius' rule of QXT).

Davison⁷ employed the technic used by Northrop and Hussey to determine diastatic activity, using a boiled, autoclaved, buffered solution of starch two and a half times more viscous than water and obtained for diastase results similar to those which were obtained by Northrop and Hussey for trypsin and pepsin. Maslow and Davison⁸ compared the viscosimetric with other accepted methods for determination of the activity of diastase, and found that the results checked fairly well. O'Donovan and Davison,⁹ using the viscosimetric method, could show the presence in the blood of the normal amylase-accelerator.

The viscosimetric method apparently has advantages over methods that preceded it in that it allows of objective control of more conditions during the determination. The technic used in our work was that advocated by Elman and McCaughan.¹⁰

Our object was to determine whether, in patients with known or suspected pancreatic disease, we could detect changes in the concentrations of amylase in the blood which might be of diagnostic significance. Elman and McCaughan observed that the amylase in the blood of normal animals was comparatively uniform in amount. In animals with experimentally produced obstruction of the pancreatic ducts, the amylase rose, within a few days, to high levels and then gradually fell. This observation had been made before.

We observed patients who were in the hospital for known or suspected pancreatic disease. In order to check the results being

6. Northrop, J. H., and Hussey, R. G.: A Method for the Quantitative Determination of Trypsin and Pepsin, *J. Gen. Physiol.* **5**:353 (Jan.) 1922-1923.

7. Davison, W. C.: A Viscosimetric Method for the Quantitative Determination of Amylase, *Bull. Johns Hopkins Hosp.* **37**:281, 1925.

8. Maslow, E. L., and Davison, W. C.: A Comparison of the Viscosimetric Copper Reduction, Polariscope, and Iodometric Methods for Measuring the Rate of Hydrolysis of Starch and Dextrin by *Aspergillus Oryzae*, *J. Biol. Chem.* **68**:75 (April) 1926.

9. O'Donovan, Charles, Jr., and Davison, W. C.: The Amylase-Accelerator and Anti-Trypsin of Normal Human Serum, *Bull. Johns Hopkins Hosp.* **40**:238, 1927.

10. Elman, Robert; and McCaughan, J. M.: The Quantitative Determination of Blood Amylase with the Viscosimeter, *Arch. Int. Med.* **40**:58 (July) 1927.

obtained, from time to time determinations were made on patients without suspected pancreatic disease or on normal subjects. Values for amylase in five normal subjects were respectively 4.2, 6.0, 7.0, 5.1 and 7.2. The values for amylase are expressed in units that indicate a quantity of amylase that will effect, in one hour, a change of 20 per cent

TABLE 1.—*Amount of Amylase in Blood in Pancreatic Diseases*

Case	Age, Yrs.	Sex*	Diagnosis	Symptoms	Amylase, Units
1	44	♂	Subacute cholecystitis, cholelithiasis, hemorrhagic pancreatic cyst, fat necrosis	Symptoms of peptic ulcer for fifteen years; ruptured duodenal ulcer, three months previously; pneumonia; nausea for six weeks; no pain	15.1
2	61	♂	Obstructive jaundice, carcinoma of pancreas	Epigastric distress for three months; painless jaundice for ten days	5.6
3	45	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for six weeks.....	5.1
4	41	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for seven weeks.....	7.1
5	52	♂	Obstructive jaundice, carcinoma of pancreas	Weakness for four months; chills and fever for two months; jaundice for ten days	75.0
6	63	♀	Obstructive jaundice, carcinoma of pancreas with metastasis to liver	Nausea for two weeks; jaundice for one week	4.2
7	43	♀	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for four months; severe pruritus for five weeks	3.2
8	64	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice two years previously; cholecystoduodenostomy twenty-two months previously	3.5
9	72	♀	Obstructive jaundice, carcinoma of pancreas	Indigestion one year; diarrhea three months; painless jaundice one month	1.7
10	49	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice six weeks.....	3.2
11	43	♂	Obstructive jaundice, carcinoma of pancreas	Onset of jaundice with epigastric pain seven months previously; jaundice with only occasionally some epigastric pain for six months	3.2
12	60	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for five weeks; chills and fever for four weeks	4.0
13	46	♂	Stone in common bile duct, pancreatitis, enlargement and induration of head of pancreas and surrounding tissue	Chills for four months; fever and glycosuria at times	4.6
14	38	♂	Carcinoma at ampulla of Vater, obstructive jaundice	Painless jaundice for three and a half months; pruritus for three months	38.0
15	72	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for two months; pruritus for six weeks	3.8
16	55	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for six weeks; diarrhea for three weeks	8.0
17	64	♂	Obstructive jaundice, carcinoma of pancreas	Painless jaundice for seven weeks; severe pruritus for six weeks	5.0
18	45	♀	Cyst in pancreas.....	Severe epigastric pain for seven months, collapse, shock, in bed for three months	53.0
19	52	♀	Obstructive jaundice, carcinoma of pancreas	Jaundice for five weeks; pruritus for four weeks	12.3
20	47	♀	Obstructive jaundice, carcinoma of pancreas	Jaundice for eighteen months; pruritus and diarrhea for fifteen months	3.5

* In this column, ♂ stands for male; ♀, female.

in the viscosity of 5 cc. of a 7 per cent buffered solution of starch. Special preparations were not made. Blood for determinations of amylase was drawn at any convenient time during the day, as it has been shown that values for amylase in blood are remarkably constant and apparently are not influenced by intake of food.

In table 1 are shown the results of determinations on twenty patients with known pancreatic disease. The age and sex did not have any

relation to the results. The clinical and surgical diagnoses usually agreed, but in table 1 the condition found at the time of operation is given. A note as to the duration and nature of the disease is included. In cases 1, 5, 14, 18 and 19, the amounts of amylase are definitely increased (normal values are from about 4 to 8 units). In these five cases there is nothing in the case histories or in the records of surgical examination that is particularly significant or different from other cases, except in case 18. In this case, the illness of the patient, a woman, dated from an acute attack of pain in the upper part of the abdomen which was followed immediately by collapse; this had occurred six

TABLE 2.—*Amount of Blood Amylase in Various Diseases*

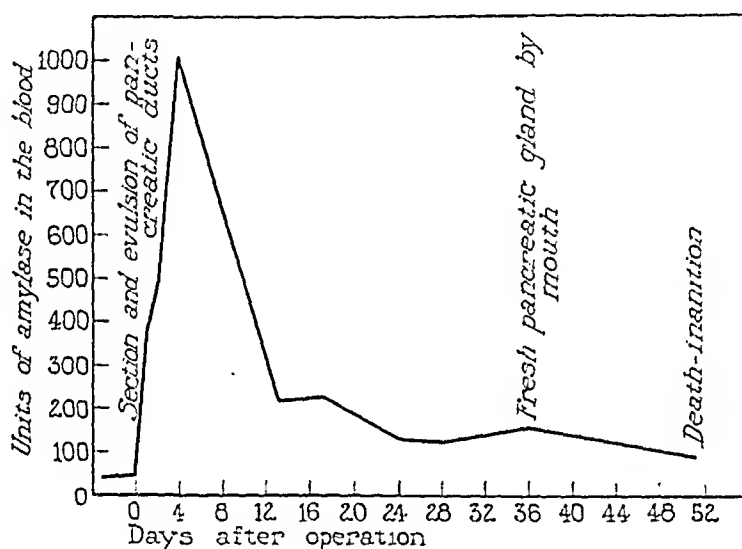
Case	Diagnosis	Amylase, Units
1	Obesity, psychoneurosis, migraine.....	8.5
2	Chronic infectious arthritis.....	4.2
3	Catarrhal jaundice.....	2.6
4	Diabetes mellitus, dwarfism.....	15.7
5	Diabetes mellitus, catarrhal jaundice.....	5.9
6	Diabetes mellitus, obesity.....	4.0
7	Obstructive jaundice, stone in common bile duct.....	3.9
8	Adenomatous goiter, hyperthyroidism, catarrhal jaundice.....	3.7
9	Diabetes mellitus, chronic cholecystitis, obesity.....	3.4
10	Chronic diffuse nephritis, hypertension, myocardial failure.....	4.8
11	Catarrhal jaundice.....	5.6
12	Biliary cirrhosis, splenomegaly.....	3.2
13	Obstructive jaundice, cholecystitis with stones.....	3.3
14	Diabetes mellitus, obstructive jaundice, stone in common bile duct.....	3.5
15	Diabetes mellitus, cholecystitis with stones.....	3.3
16	Obstructive jaundice, stone in common bile duct.....	4.1
17	Cirrhosis of the liver, stricture of common bile duct.....	3.1
18	Chronic nervous exhaustion, mucous colitis.....	6.2
19	Diabetes mellitus, pituitary tumor (acromegaly), latent syphilis.....	24.0
20	Carcinoma of stomach with pyloric obstruction.....	1.3
21	Hypoglycemia.....	3.0
22	Essential arterial hypertension, vasomotor instability, neurosis, erythromelalgia, transient glycosuria.....	1.8
23	Chronic nervous exhaustion.....	4.6
24	Obstructive jaundice, stricture of the common bile duct.....	3.4
25	Pott's disease, diabetes mellitus.....	1.8
26	Carcinoma of stomach.....	3.5
27	Duodenal ulcer.....	4.6
28	Obstructive jaundice, stone in common bile duct.....	4.1
29	Chronic nervous exhaustion.....	3.2
30	Duodenal ulcer.....	2.8

months before she had come to the clinic. She had improved slowly after the pain and collapse, but had been confined to her bed practically all the time since then. She had had some epigastric pain, but the main feature of her illness was weakness, with progressive abdominal enlargement. At operation, a large pancreatic cyst was found and drained.

Table 2 shows the results obtained in thirty patients with various diseases, many of whom had diabetes mellitus. The only two patients in this group with elevated amounts of amylase were a dwarf (case 4), and a patient with acromegalia (case 19), both of whom had diabetes mellitus. The patient with acromegalia died in the hospital, and at necropsy a pituitary tumor was found. Nothing remarkable was found in the pancreas.

COMMENT

In general, the results of our studies were similar to those obtained by Elman.¹¹ He reported determinations of amylase on thirty patients without pancreatic disease. His results were fairly uniform. In two cases of pancreatic cysts and one of acute pancreatitis, values for amylase in the blood were elevated. In our series of twenty patients with known pancreatic tumor, there were two with pancreatic cysts, and in both the values for amylase in the blood were elevated. In only four of the twenty were there increased amounts of amylase. Elman has reported one case of carcinoma of the pancreas with a value for amylase in the blood of 0.5 unit. We did not observe a value as low in any patient. In case 8 (table 1) carcinoma of the pancreas had been present for more than two years.



Amylase in blood of experimental animal.

The increase in the amount of amylase in the blood of the two patients represented in table 2 brought up the question as to the source of the amylase. It is found in a number of tissues in the body other than the pancreas and salivary glands. In 1913 Macleod¹² showed, however, that the amount of diastase was greater in the blood than in other organs and concluded that the gradient of pressure was from the pancreas to the blood. Elman and McCaughan did not observe variations in the amount of amylase in the blood after several days of total drainage to the outside of the pancreatic juice. This is taken to indicate that intestinal absorption of amylase does not play a demonstrable part in maintaining the normal levels of amylase in the blood.

11. Elman, Robert: The Blood Amylase in Pancreatic Disease, *Proc. Soc. Exper. Biol. & Med.* 25:173, 1927-1928.

12. Macleod, J. J. R.: *Diabetes: Its Pathological Physiology*, London, E. Arnold, 1913, p. 151.

Not enough is known about the origin and physiologic function of diastase to attempt explanation of increases or decreases of the amount of amylase in the blood in health. Under abnormal conditions, such as complete obstruction of the pancreatic duct produced by ligation, the amylase in the blood is definitely increased. This increase is of definite duration in the experimental animal, and is much higher than that which has been observed under any other circumstances. One of us (McCaughan) obtained the data shown in the accompanying chart. The major and minor pancreatic ducts of a dog were sectioned and evulsed. The possibility of the existence of accessory ducts was excluded by careful search. On the fifty-first day after operation, the animal died. Postmortem examination did not disclose any other cause for death than the inanition incident to the complete loss of pancreatic digestion. The reading obtained just prior to death was about double that of the preoperative level. This suggests that the value of the study of blood amylase as a diagnostic test in pancreatic disease is limited by two factors: The estimations must be made within a comparatively short time after the occurrence of obstruction of the ducts, and the obstruction must be of sufficient degree that absorption of the amylase by the blood stream will yield values far enough beyond the normal range to be of definite significance. It is also suggested that values much below the normal may occur when complete atrophy of the gland follows long continued total obstruction; naturally, the declining curve may at some time or other again fall within the normal range, thus rendering proper interpretation difficult or impossible.

SUMMARY AND CONCLUSIONS

In a group of twenty patients known to have pancreatic tumors, the values for amylase in the blood were increased in six and normal in fourteen.

In a group of thirty patients suffering from various diseases, the values for amylase in the blood were increased in two.

Blood amylase values were found increased in two patients, with anomalies of growth, namely, dwarfism and acromegalia. This suggests a possible relationship between increased blood amylase values and pituitary dysfunction.

Although the series of clinical cases studied is small, it seems probable that the percentage of positive data in pancreatic disease would be similar in a larger series. The percentage is too small to warrant the adoption of a routine diagnostic procedure of study of the amylase of the blood in cases of suspected pancreatic disease.

Book Reviews

TULAREMIA. HISTORY, PATHOLOGY, DIAGNOSIS AND TREATMENT. By WALTER M. SIMPSON, M.S., M.D., Director of the Diagnostic Laboratory, Miami Valley Hospital, Dayton, Ohio. Foreword by Edward Francis, Surgeon U. S. Public Health Service. Price, \$5. New York: Paul B. Hoeber.

It is fitting that information on this widespread new disease should be collected and published in book form. The author calls attention to the service rendered by the United States Public Health Service in discovering and accurately determining the sources of infection and the means of diagnosing this disease. Fifteen Public Health Service laboratory workers have contracted tularemia. The earliest written description of tularemia in man appears in a letter written in 1904 by a boy of 15 years to his sister, describing an illness which he attributed to contact with rabbits.

During at least thirty years meat handlers had recognized the characteristic lesion of tularemia which they called "rabbit fever." He describes the tireless work of Dr. Edward Francis in studying the various sources of infection. This historical chapter furnishes most interesting reading.

A chapter is devoted to the zoologic distribution of tularemia, with a long list of mammals and insects that may act as carriers of the infection.

Chapter 5 is devoted to the clinical manifestation of tularemia, including its distribution. Cases have now been reported from every state except the states in New England, Delaware and Washington, with Ohio holding first place, almost certainly due to the efforts of the author. The various clinical manifestations of the disease are described clearly and are illustrated profusely with excellent photographic reproductions.

Chapter 6 is devoted to the pathology of tularemia. Here, as in the preceding chapter, a clear text is further elucidated by suitable illustrations.

Chapter 7 is given over to the bacteriology of tularemia.

Chapter 8 presents in an interesting manner the serology of tularemia. Agglutination which reaches its maximum during the third week shows a high titer, 1:1,280 or 1:256. Agglutination still occurs in a lower titer after the lapse of twenty years.

The final chapter is devoted to treatment, followed by an extensive bibliography.

The style in which this book is written makes it fascinating reading. The print is large and the illustrations are good. The reviewer has much to commend and nothing to criticize.

MEDIZINISCHE PRAXIS. Sammlung für Ärztliche Fortbildung. Volume VII. Der Sogenannte Rheumatismus. By DR. JULIUS BAUER, Professor at the University of Vienna. Price, 10.50 Rm. Dresden: Theodor Steinkopff, 1929.

The object of this series of monographs is to furnish practical information to the physician. This volume contains little that is new and is of limited value as an aid to acquiring knowledge of this little understood disease.

The author discusses acute arthritis, chronic arthritis, myalgia and neuralgia. Myalgia and neuralgia are discussed as conditions distinct from chronic arthritis. It is highly probable that neuralgia is a root pain secondary to spinal osteoarthritis. In discussing chronic arthritis, instead of using the expression atrophic arthritis or rheumatoid arthritis, he uses the term chronic polyarthritis—considering the process an inflammatory one. This is in accord with the prevailing view in this country. He considers osteoarthritis a disease of years, as each decade after twenty years shows an increasing frequency. In this he is in accord

with the widely accepted belief in this country that the disease is a degenerative rather than an infectious process.

The illustrations are good, and there is a limited bibliography.

DIET AND EFFICIENCY. A FIVE-YEAR CONTROLLED EXPERIMENT ON MAN.
By HAROLD H. G. HOLCK. Price, \$1.00. Chicago: University of Chicago Press.

Experimental studies such as this are all too rare in the field of dietetics. As Carlson says in the preface, "Scientific knowledge of the relation of the diet to health and efficiency . . . has played little or no rôle in human evolution." Fads have been followed as facts; newspaper and propagandist information has been accepted as truth. The experimental method applied to food and human life is difficult, but the present study seems to have overcome the major difficulties, and therefore the conclusions are of value. The problem was to study the effect of modified "fletcherizing" of food; the technic and the standards were carefully controlled. The accumulated data are too detailed to review, but the summary of results indicates that "fletcherizing" decreased muscular endurance, typewriting accuracy and basal metabolism, and that it had no effect on blood pressure, pulse rate, oral temperature, sleeping time, mental multiplication and typewriting speed. Improvement in efficiency in solving chess problems was noted, and the rather high body weight was lowered to a more nearly normal standard.

OUTLINE OF PREVENTIVE MEDICINE FOR MEDICAL PRACTITIONERS AND STUDENTS. Prepared under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine. Cloth. Price, \$5. Pp. 398. New York: Paul B. Hoeber, Inc., 1929.

This is a medium sized, flexible leather bound volume, consisting of twenty-one chapters and an index, each chapter of which has been contributed by a well qualified specialist. It was prepared particularly for use by general practitioners and students of medicine, whose "usual attitude toward preventive medicine is, of course, commendatory but not exactly enthusiastic"; also, it has been written primarily to arouse their interest in preventive medicine and periodic health examinations, thereby meeting a demand which the public has been educated to make. Closer cooperation by the general practitioner and specialist with health boards, school authorities, community social agencies, etc., is stressed.

Well written, avoiding technical terms and carefully compiled, it fills a distinct need and should prove a useful guide.

RHEUMAPROBLEME, GESAMMELTE VORTRÄGE. By VARIOUS AUTHORS. Price, 12 marks. Pp. 181, with 55 illustrations including 4 colored plates. Leipzig: Georg Thieme, 1929.

This volume contains the initial series of lectures that were delivered at the Rheuma-Forschungs-Institut am Landesbad der Rheinprovinz in Aachen, Oct. 18-20, 1928. Chronic arthritis, muscular rheumatism and rheumatic fever all are dealt with from the pathologic, clinical and therapeutic points of view. Most of the chapters contain admirable summaries of the present knowledge and ignorance of the particular field discussed. The chapter by Fritz Gudzent on the chronic arthritides is especially to be recommended for its conservatism and conciseness. Hugo Schottmüller's contribution on rheumatic fever is excellent.

PROLONGED TREATMENT OF EXOPHTHALMIC GOITER BY IODINE ALONE*

WILLARD OWEN THOMPSON, M.D.

Henry P. Walcott Fellow in Clinical Medicine, Harvard Medical School

PHEBE K. THOMPSON, M.D.

ALLEN G. BRAILEY, M.D.

AND

ARCHIBALD C. COHEN, A.B.

BOSTON

The value of a short intensive course of iodine medication as a method of preparing a patient with exophthalmic goiter for thyroidectomy has been unquestioned since the report of Plummer¹ in 1923. Following his announcement, the use of iodine in this disease rapidly became widespread. It was soon noted by various observers, beginning with Starr, Segall and Means,² that in cases in which this medication was prolonged, its effect, though striking, was usually only temporary; and that after a few weeks the patient might be as ill as before it was started, if not worse. Thus, in general, the prolonged treatment for exophthalmic goiter with iodine alone has come to be regarded as a futile, if not a dangerous, procedure.

There are, however, some observations in the literature concerning favorable results in exophthalmic goiter with this method of treatment. Trousseau,³ in 1863, mentioned a patient in whom the disease was "singularly improved by the prolonged administration of iodide of potassium." Cheadle,⁴ in 1869, reported satisfactory improvement maintained for periods of nine and three months, respectively, in two of seven well marked cases; in none of the other five cases was the disease aggravated. Ohlemann,⁵ in 1911, claimed that he was cured

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* From the Thyroid Clinic and Metabolism Laboratory, Massachusetts General Hospital.

1. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, *J. A. M. A.* **80**:1955 (June 30) 1923.

2. Starr, P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, *Arch. Int. Med.* **34**:355 (Sept.) 1924.

3. Trousseau, A.: Lectures on Clinical Medicine, translated by P. V. Bazire, London, The New Sydenham Society, 1868, vol. 1, p. 586.

4. Cheadle, W. B.: Exophthalmic Goitre, *St. George Hosp. Rep.* **4**:175, 1869.

5. Ohlemann: Zur Iodbehandlung bei der Basedow'schen Krankheit, *Berl. klin. Wchnschr.* **48**:385, 1911.

of exophthalmic goiter after three years' treatment with iodine. Marine and Lenhart,⁶ in 1911, observed that complete involution of the thyroid to the colloid state occurred in four patients with exophthalmic goiter who were treated with iodine for periods of from two to eighteen months, and that there were no injurious effects. Neisser,⁷ in 1920, reported control of the disease for periods of from one and one-half to two years in three patients. Beebe,⁸ in 1921, referring to patients with typical exophthalmic goiter, said that "small doses . . . rarely cause any disturbing reaction and if continued with occasional interruptions over some weeks or months it appears to the writer to be of benefit for the majority." Jagić and Spengler⁹ and Mason,¹⁰ in 1924, each noted a similar effect for seven months in one patient; and Cowell and Mellanby,¹¹ for five months in one of a series of eight patients. Plummer,¹² in 1925, said that some of his patients had been "controlled continuously for more than two years except for short periods during which the administration of iodine was stopped to determine the necessity of continuing it." Mellanby,¹³ in 1925, observed that after two years or more of treatment with iodine many patients could lead normal lives and be regarded as cured. He thought that the chief dangers of prolonged iodine medication were in administering it to patients with large hard thyroids. Fraser,¹⁴ in 1925, said that "some patients" would respond satisfactorily to small doses of iodine almost indefinitely, particularly if they could lead sheltered lives; but he found that in most cases the improvement did not persist. Kohlmann,¹⁵ in 1925, noted improvement lasting at least one year in one

6. Marine, D., and Lenhart, C. H.: *Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment*, Arch. Int. Med. **8**:265 (Sept.) 1911.

7. Neisser, E.: *Ueber Jodbehandlung bei Thyreotoxikose*, Berl. klin. Wchnschr. **57**:461, 1920.

8. Beebe, S. P.: *Iodine in the Treatment of Goiter*, M. Rec. **99**:996, 1921.

9. Jagić, N., and Spengler, G.: *Weitere Beobachtungen über Jodwirkung bei Strumen*, Wien. klin. Wchnschr. **37**:116, 1924.

10. Mason, E. H.: *Iodine Therapy in Toxic Goitre*, Tr. Assoc. Am. Phys. **39**:167, 1924.

11. Cowell, S. J., and Mellanby, E.: *The Effect of Iodine on Hyperthyroidism in Man*, Quart. J. Med. **18**:1, 1924-1925.

12. Mayo, C. H., and Plummer, H. S.: *The Thyroid Gland*, part 2, St. Louis, C. V. Mosby Company, 1926, p. 76.

13. Mellanby, E.: *Discussion on the Treatment of Exophthalmic Goitre: Iodine Therapy of Exophthalmic Goitre*, Proc. Roy. Soc. Med., Sects. Surg. Med. Electro-Therap. & Therap. **19**:101 (June) 1926.

14. Fraser, F. R.: *Iodine in Exophthalmic Goitre*, Brit. M. J. **1**:1, 1925.

15. Kohlmann, M.: *Kasuistischer Beitrag zur Behandlung des Morbus Basedowii mit kleinen Joddosen*, München. med. Wchnschr. **72**:226, 1925.

patient on iodine. Foster,¹⁶ in 1925, remarked that "while some patients continue to take iodine the symptoms and signs of the disease are definitely ameliorated for as long as three years." He regarded the use of iodine as an experiment in each case and said that a systematic study of the question was much to be desired. Labbé,¹⁷ in the same year, in a series of ten cases observed three apparent "cures" during the administration of iodine for a maximum of six months. Cole,¹⁸ in 1927, reported a series of nineteen cases of hyperthyroidism in which iodine was given. Three cases showed no tendency to relapse after continuous treatment for five months. Goetsch,¹⁹ in 1927, said that he had seen a few satisfactory results in very early cases, but that he had abandoned the use of iodine except as a preoperative measure in advanced cases, on account of uniformly bad results.

During the past three years at the Massachusetts General Hospital, we have collected data on a series of twenty-four patients with exophthalmic goiter, most of whom were followed closely with basal metabolism determinations while undergoing prolonged treatment with iodine alone in the outpatient department. These observations seem worth reporting, in view of the present scarcity of such studies.

DATA

The results are summarized in the accompanying table.

Detailed data showing the different types of response are recorded in charts 1 to 10.

In fourteen instances this type of treatment was used because the disease was mild; this group is therefore selected. In the ten others, it was used because, although the disease was moderately severe or severe, operation was at first refused in most instances; this group is, in a sense, unselected.

The Benedict-Roth apparatus and Aub-DuBois standards were used in the determination of the basal metabolic rates. Administration of iodine was not started until two or more determinations which checked satisfactorily were made.

Iodine was used in the form of the compound solution.

16. Foster, N. B.: The Medical Treatment of Hyperthyroidism, *Am. J. Surg.* **39**:293, 1925.

17. Labbé, M.: Le traitement de la maladie de Basedow par l'iode, *J. de méd. de Paris* **46**:931, 1926.

18. Cole, L. B.: The Use of Lugol's Iodine in Exophthalmic Goitre, *Lancet* **1**: 812, 1927.

19. Goetsch, E.: The Use and Misuse of Iodine in the Treatment of Toxic Goiter, *New York State J. Med.* **27**:1075, 1927.

Response to Prolonged Treatment with Iodine Alone in Twenty-Four Patients with Exophthalmic Goiter

Case	Description	Before Iodine Was Started		Last Observation on Iodine		Duration of Iodine Medication	Comment
		Clinical Condition	Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Clinical Condition	Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight		
1	See chart 1 Lab. No. 3513	Mild exophthalmic goiter	No thyrotoxicosis		
2	See chart 2 Lab. No. 4906	Mild exophthalmic goiter	No thyrotoxicosis		
3	See chart 3 Lab. No. 4034	Mild exophthalmic goiter	No thyrotoxicosis		
4	Miss H. J., a housemaid, aged 19 Lab. No. 5183	Mild exophthalmic goiter; goiter + bruit ++ exophthalmos 0 tremor ++ sweating ++ nervousness ++ weight loss 0	+33, 7 tests Pulse 96 Wt. 56.3 Kg.	No thyrotoxicosis; goiter 0 bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	+16 Pulse 66 Wt. 51.9 Kg.	On compound solution of iodine, from 1/4 to 1 drop daily, continuously, for 5 1/2 months; 9 tests	The basal metabolic rate dropped to +14 per cent within 3 weeks after starting iodine medication; there was marked clinical improvement and gradual disappearance of thyrotoxicosis; when last seen, the patient had been without iodine for 10 months; the basal metabolic rate was +4 per cent and there was no evidence of recurrence of thyrotoxicosis (5 tests)
5	See chart 4 Lab. No. 5663	Mild exophthalmic goiter	No thyrotoxicosis		
6	Mrs. M. H., a housewife, aged 65 Lab. No. 5470	Mild exophthalmic goiter and auricular fibrillation; goiter + bruit 0 exophthalmos ++ tremor + sweating + nervousness ++ weight loss ++	Pulse 106, fibrillating Wt. 40.1 Kg.	No thyrotoxicosis or auricular fibrillation; goiter + bruit 0 exophthalmos + tremor 0 sweating normal nervousness +	Pulse 70, regular Wt. 48.6 Kg.	On compound solution of iodine, 1 drop daily, continuously, for 14 months	Marked improvement in symptoms occurred within 2 weeks after starting iodine; this was sustained throughout the period of iodine medication, in spite of a major pelvic operation. When last seen, the patient had been without iodine for 5 1/2 weeks; there was no evidence of recurrence of thyrotoxicosis; the determinations of basal metabolism (47 tests) were worthless, owing to irregular breathing
7	Miss F. W., a school girl, aged 15 Lab. No. 5530	Mild exophthalmic goiter; goiter + bruit ++ exophthalmos + tremor + sweating ++ nervousness ++ weight loss 0	Dropped from +42 to +14 in 5 weeks (5 tests); +26 later, without iodine Pulse 116 Wt. 44.8 Kg.	No thyrotoxicosis; goiter + smaller bruit 0 exophthalmos + less tremor 0 sweating + nervousness +	+10 Pulse 84 Wt. 48.5 Kg.	On compound solution of iodine, 1 drop daily, for 1 year, with two intervening omissions of 1 month each; 11 tests	On the first two omissions of iodine, the basal metabolic rate rose from normal (-1 and +7 per cent) to +17 and +26 per cent respectively, and there was a recurrence of thyrotoxicosis; during the last course of iodine, of 4 months' duration, the basal metabolic rate again dropped to normal and thyrotoxicosis disappeared; when last seen, the patient had been without iodine for 4 months; the basal metabolic rate was +8 per cent and there was no evidence of thyrotoxicosis (3 tests)

8	See chart 5 Lab. No. 5507	Mild exophthalmic goiter	No thyrotoxicosis			
9	Mrs. V. J., a housewife, aged 41 Lab. No. 5506	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor ? sweating 0 nervousness ++ weight loss ++	+23, 3 tests Pulse 73 Wt. 40.5 Kg.	No thyrotoxicosis; goiter 0 bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	-1 Pulse 73 Wt. 40.3 Kg.	Eleven months' continuous administration of compound solution of iodine, $\frac{1}{2}$, 1, 5, 1, $\frac{1}{2}$ and $\frac{1}{10}$ drop daily, respectively (20 tests)	The basal metabolic rate dropped to normal, coincident with the disappearance of thyrotoxicosis; 1 month after iodine was started, and remained there throughout the period of observation
10	See chart 6 Lab. No. 5004	Mild exophthalmic goiter	No thyrotoxicosis			Up to 9 months after starting iodine the basal metabolic rate had dropped to only +21 per cent (3 tests); about 3½ years before this period of observation, the patient had questionable exophthalmic goiter, with a basal metabolic rate of +24 per cent; during 1 month of iodine medication there was no improvement; on omission of iodine, the basal metabolic rate rose to +43 per cent and there was definite thyrotoxicosis; about 3 months later the basal metabolic rate was -16 per cent and there was no evidence of thyrotoxicosis; she was not seen again for 3 years
11	Miss J. O'B., a stenographer, aged 31 Lab. No. 2352	Mild exophthalmic goiter; goiter ++ bruit 0 exophthalmos + tremor + sweating + nervousness ++ weight loss +	+36 Pulse 104 Wt. 47.8 Kg.	No thyrotoxicosis; goiter + bruit 0 exophthalmos + tremor 0 sweating normal nervousness +	+6 Pulse 89 Wt. 46.7 Kg.	Eleven months' continuous administration of iodine, either 1 drop of compound solution or 0.75 Gm. of potassium iodide daily in asthma medicine; sometimes both (4 tests)	During the first 3 months on iodine the basal metabolic rate did not drop, but the patient gained 3 Kg. and was slightly improved; on omission of iodine for 2 months, the basal metabolic rate rose to +40 per cent, the pulse to 124, and her weight dropped 2 Kg.; on resuming iodine medication, the basal metabolic rate promptly dropped to +15 per cent, with definite clinical improvement, remaining thus for about 10 months until iodine was omitted; then the basal metabolic rate rose to +26 per cent and she became more nervous; on resuming iodine, the rate dropped to +4 per cent; there was no evidence of thyrotoxicosis
12	Miss S. G., a school girl, aged 18 Lab. No. 5092	Mild exophthalmic goiter; goiter ++ bruit ++ exophthalmos + tremor + sweating ++ nervousness ++ weight loss 0	+22, 3 tests Pulse 93 Wt. 41.9 Kg.	No thyrotoxicosis; goiter slightly + bruit 0 exophthalmos 0 tremor 0 sweating normal nervousness +	+4 Pulse 83 Wt. 42.1 Kg.	On compound solution of iodine, usually 1 drop daily, for 1½ years, with 2 omissions of 2 months each (21 tests)	During the first 3 months on iodine the basal metabolic rate did not drop, but the patient gained 3 Kg. and was slightly improved; on omission of iodine for 2 months, the basal metabolic rate rose to +40 per cent, the pulse to 124, and her weight dropped 2 Kg.; on resuming iodine medication, the basal metabolic rate promptly dropped to +15 per cent, with definite clinical improvement, remaining thus for about 10 months until iodine was omitted; then the basal metabolic rate rose to +26 per cent and she became more nervous; on resuming iodine, the rate dropped to +4 per cent; there was no evidence of thyrotoxicosis
13	Mr. R. S., a gardener, aged 46 Lab. No. 5398	Moderately severe exophthalmic goiter; goiter * sweating +++ nervousness +++ weight loss +++ appetite ++ Palpitation and dyspnea +	+40, 2 tests Wt. about 70 Kg.	Very mild exophthalmic goiter; goiter + bruit 0 exophthalmos 0 tremor 0 sweating + nervousness +	+21 Pulse 70 Wt. 78.6 Kg.	One year continuously on compound solution of iodine, 30 drops daily, and then 30 drops daily twice a week (2 tests)	Marked improvement in symptoms and a gain of 20 pounds in weight occurred within 3 months after starting iodine; the patient was first seen in this clinic about 10 months after starting iodine; the basal metabolic rate was +23 per cent, but the patient showed little evidence of thyrotoxicosis

* Size unknown.

Case	Description	Before Iodine Was Started		Last Observation on Iodine		Duration of Iodine Medication	Comment
		Clinical Condition	Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight	Clinical Condition	Basal Metabolic Rate, per Cent of Normal; Pulse Rate; Weight		
14	Mrs. E. C., a housewife, aged 35 Lab. No. 4075	Mild exophthalmic goiter; goiter + bruit + exophthalmos + tremor + sweating + nervousness ++ weight loss ++	+24.2 tests Pulse 104 Wt. 47.9 Kg.	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor + sweating + nervousness ++	+19 Pulse 87 Wt. 49.0 Kg.	There were 3 courses of compound solution of iodine, of 1, 4 and 9 months' duration respectively, with 2 intervening omissions of 2 months each; the dose varied from $\frac{1}{2}$ to 30 drops daily (33 tests)	The first course of compound solution of iodine had little clinical effect; the basal metabolic rate dropped to +15 per cent and rose, on omission of iodine, to +26 per cent; the second course of iodine had a prompt and striking effect, finally producing a clinical condition suggesting mild myxedema, with a basal metabolic rate of —15 per cent; on omission of iodine, the basal metabolic rate rose to +21 per cent and thyrotoxicosis recurred; during the third course of iodine the basal metabolic rate promptly fell to normal, with some clinical improvement; the patient remained thus for about 7 months; during the next 2 months on iodine the basal metabolic rate rose to +19 per cent and the patient felt as ill, but no worse, than before iodine medication was started
15	Mrs. A. H., a housewife, aged 37 Lab. No. 5917	Mild exophthalmic goiter; goiter + bruit + exophthalmos + tremor + sweating ++ nervousness ++ weight loss +	Dropped from +26 to +12 on rest in bed; 4 tests Pulse 72 Wt. 45.8 Kg.	Mild exophthalmic goiter; goiter + bruit 0 exophthalmos + tremor 0 sweating + nervousness +	+17 Pulse 75 Wt. 47.1 Kg.	On compound solution of iodine, from 30 to 5 drops daily, for $1\frac{1}{2}$ months continuously (4 tests)	The basal metabolic rate fell to —7 per cent, with corresponding clinical improvement, while the patient was in the hospital, within 1 week after starting iodine; the patient was then discharged; about 5 weeks later her basal metabolic rate was +17 per cent and thyrotoxicosis was recurring (only on omission of iodine did the basal metabolic rate rise to 46 per cent and the patient become worse than initially)
16	Mr. E. S., a factory worker, aged 35 Lab. No. 6251	Moderately severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor + sweating ++ nervousness ++ weight loss ++	+50, 3 tests Pulse 98 Wt. 55.5 Kg.	Moderately severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor + sweating + nervousness ++	+44 Pulse 96 Wt. 55.7 Kg.	After 3 months continuously on compound solution of iodine, 1 drop daily (6 tests)	The basal metabolic rate fell to +13 per cent with definite clinical improvement within 2 weeks after starting iodine; it then rose gradually to +57 per cent within another 5 weeks, before dropping to the final +44 per cent; thyrotoxicosis recurred, but the patient was no worse at any time than before iodine was started
17	Miss A. P. Y., a factory worker, aged 21 Lab. No. 4822	Severe exophthalmic goiter; goiter ++ bruit ++ exophthalmos 0 tremor ++	+72, 2 tests Pulse 131 Wt. 51.7 Kg.	More severe exophthalmic goiter; goiter ++ bruit ++ exophthalmos 0 tremor ++	+80 Pulse 122 Wt. 56.1 Kg.	4½ months continuously on compound solution of iodine, 1, 15, 80, 1, 30, 90 and 1 drop daily, respectively (33 tests)	The basal metabolic rate fell to +27 per cent within 10 days after starting 1 drop of compound solution of iodine; about 3 weeks later, on 30 drops, it fell to +16 per cent; there was marked clinical improvement; after this the basal metabolic rate gradually rose on 30 drops and continued to rise

		sweating ++ nervousness ++ weight loss ++	sweating +++ nervousness +++		on 1 drop of compound solution of iodine until, 3 months after starting iodine medication, it was +58 per cent; on 30 and 90 drops, it fell to +33 per cent, but on reducing the dose 3 weeks later to 1 drop, it gradually rose to +80 per cent; at this point the thyrotoxicosis was more marked than before iodine was started; the patient was completely refractive to 1 drop of compound solution of iodine daily, because when this was omitted, the basal metabolic rate did not rise significantly, but within 2 months decreased spontaneously to +65 per cent; at this time 1 drop of compound solution of iodine daily produced a typical remission
18	See chart 7 Lab. No. 5168	Moderately severe exophthalmic goiter	Severe exophthalmic goiter	
19	See chart 8 Lab. No. 6414	Moderately severe exophthalmic goiter	Severe exophthalmic goiter	
20	Mrs. E. C., a housewife, aged 52 Lab. No. 5068	Moderately severe exophthalmic goiter; + very firm bruit 0 exophthalmos 0 tremor ++ sweating +++ nervousness +++ weight loss ++	+38, 6 tests Pulse 100 Wt. 57.0 Kg.	Moderate but less severe exophthalmic goiter; goiter + very firm bruit 0 exophthalmos 0 tremor 0 sweating ++ nervousness ++	+29 Pulse 91 Wt. 61.6 Kg. 7½ months on compound solution of iodine, from ½ to 1 drop daily, with one omission of 1½ months (8 tests)
21	Mr. A. B., a telegrapher, aged 35 Lab. No. 6312	Moderately severe exophthalmic goiter; goiter + bruit ? exophthalmos 0 tremor ++ sweating ++ nervousness ++ weight loss ++	Dropped from +45 to +29 on rest in bed; 6 tests Pulse 102 Wt. 51.9 Kg.	Moderate but less severe exophthalmic goiter; goiter + bruit 0 exophthalmos 0 tremor + sweating + nervousness + Less severe exophthalmic goiter	+37 Pulse 101 Wt. 57.9 Kg. On compound solution of iodine, from 1 to 2 drops daily, for 2 months continuously (4 tests)
22	See chart 9 Lab. No. 6102	Severe exophthalmic goiter	Less severe exophthalmic goiter	
23	Mr. I. C., a salesman, aged 41 Lab. No. 5067	Severe exophthalmic goiter; goiter + bruit + exophthalmos ++ tremor ++ sweating + nervousness ++ weight loss ++	+57, 12 tests Pulse 114 Wt. 70.9 Kg.	More severe exophthalmic goiter; goiter + bruit ++ exophthalmos ++ tremor ++ sweating +++ nervousness ++	+77 Pulse 113 Wt. 68.2 Kg. On 1 drop of compound solution of iodine daily for 3 months continuously (5 tests)
24	See chart 10 Lab. No. 5181	Severe exophthalmic goiter	More severe exophthalmic goiter	

The symptomatic improvement on compound solution of iodine was gradual and sustained, in spite of an intercurrent illness, but was not sufficient to be satisfactory; all basal metabolic rate determinations but one (+23 per cent), during iodine medication, were +29 per cent and above

Iodine was started on discharge from the hospital; within 2 weeks, although the basal metabolic rate was unchanged (+23 per cent), the patient had gained 5 Kg., was less nervous and slept better; 2 weeks later the basal metabolic rate was +35 per cent, and he had gained an additional 2 Kg.; the basal metabolic rate did not fall below this level subsequently, and he did not gain any more weight

The basal metabolic rate did not drop significantly on compound solution of iodine, but gradually rose; the thyrotoxicosis became more marked; on omission of iodine for 9 days, the basal metabolic rate remained practically unchanged; compound solution of iodine then reduced it to +42 to +52 per cent and the patient was operated on

Types of Response.—Satisfactory: Nine cases responded satisfactorily to prolonged iodine medication as follows:

1. In four the disease apparently came to an end during or shortly after the period of treatment with iodine. This is indicated by the fact that for periods of from ten to sixteen months after iodine was omitted, the basal metabolic rate remained at a standard normal level or below and there was no clinical evidence of recurrence of thyrotoxicosis (cases 1, 2, 3 [charts 1, 2 and 3] and 4 [table]).

2. In the five others, during periods of continuous iodine medication ranging from ten to fourteen months in four cases and from one to four months intermittently for one year in one case, the disease

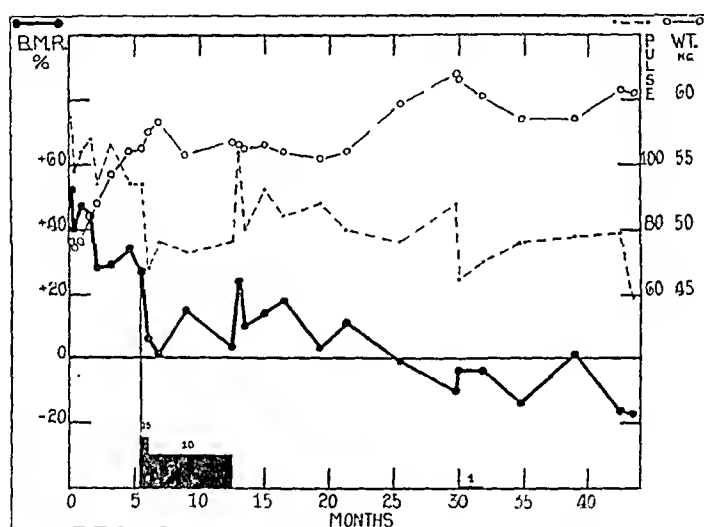


Chart 1 (case 1, lab. no. 3513).—Mrs. A. V. B., a housewife, aged 25, in whom control of signs and symptoms of mild exophthalmic goiter was secured by administration of iodine for seven months during a spontaneous retrogression of the disease (which did not appear to be hastened by the medication). At the time treatment with iodine was started: goiter +, bruit 0, exophthalmos +, tremor +, sweating +, nervousness ++. At the time of the last observation on iodine: thyroid just palpable, bruit 0, exophthalmos 0, tremor very slight, sweating normal, nervousness +. From five to seven months after omitting the first course of iodine there was no tremor and the patient was not nervous. She remained normal during the rest of the period of observation. In this and the accompanying charts, the black areas along the bottom indicate periods of treatment with compound solution of iodine and the figures above them the dosage in drops.

was at least kept satisfactorily under control with a normal basal metabolism (cases 5 [chart 4], 6, 7 [table], 8 [chart 5] and 9 [table]). In the first three cases iodine was omitted for four, five and seventeen weeks respectively, with no recurrence of symptoms; in the last two cases it was not omitted.

Fairly satisfactory: In four cases the response to prolonged iodine medication was fairly satisfactory. The results may be summarized as follows:

1. During continuous iodine medication for one and two-thirds years, the disease was again under control with a normal basal metabolism, after two prolonged complete remissions and two mild relapses (case 10 [chart 6]).

2. The disease was satisfactorily controlled, with a normal basal metabolism, only after nine months of continuous iodine medication in one case, and after eighteen months of intermittent iodine medication in another. However, during most of the periods of incomplete control, the patients were markedly improved and at no time did they become worse on iodine (cases 11 and 12 in table).

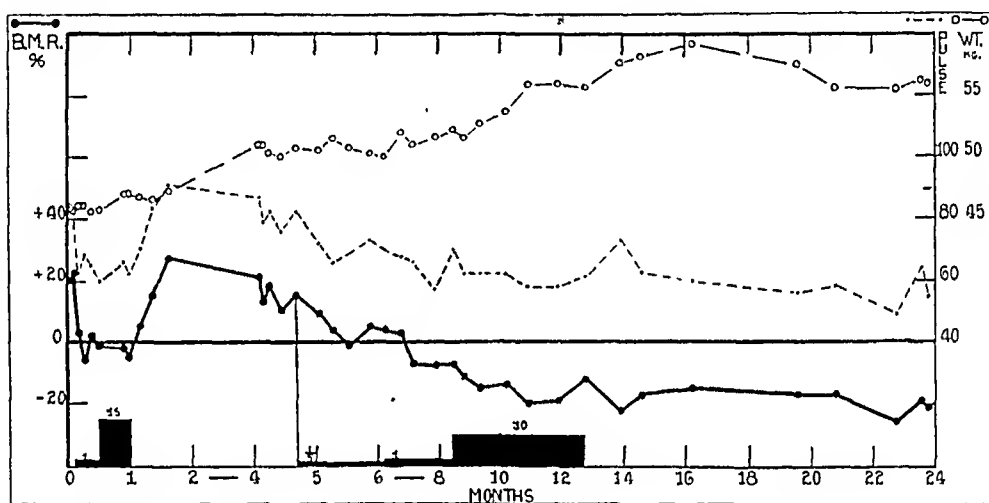


Chart 2 (case 2, lab. no. 4906).—In Mrs. E. F., a housewife, aged 28, there was control of signs and symptoms of mild exophthalmic goiter during the first course of iodine medication, and disappearance of the disease during the second course of iodine. At the time the first course of iodine was started: goiter +, bruit +, exophthalmos ++, tremor +, sweating +, nervousness ++, weight loss ++. At the time of the last observation on the second course of iodine: thyroid just palpable, bruit 0, exophthalmos 0, tremor 0, sweating normal, nervousness +. She was apparently normal during the rest of the period of observation.

3. During one year of continuous iodine medication, there was an initial prompt and striking remission which was sustained but not quite complete. The basal metabolism did not drop below plus 21 per cent (case 13 in table).

Unsatisfactory: In eleven cases the response to prolonged iodine medication was unsatisfactory. These cases can be grouped as follows:

1. In six there was a temporary improvement, accompanied by a lowering of the basal metabolism, followed by a relapse (cases 14, 15,

16, 17 [table], 18 [chart 7] and 19 [chart 8]). In all but case 14 the improvement was of short duration. Patients 17, 18 and 19 were worse symptomatically and had a higher metabolism during the relapse than before iodine was started.

2. In three there was a gain in weight and some symptomatic improvement, but no significant change in the basal metabolic rate (cases 20, 21 [table] and 22 [chart 9]).

3. In two there was no clinical improvement and no significant decrease, but a gradual increase in the basal metabolic rate, with coincident increase in the severity of symptoms (cases 23 [table] and 24 [chart 10]).

Thus, in our series of twenty-four cases, over half of which were selected because they were mild, the results obtained during prolonged

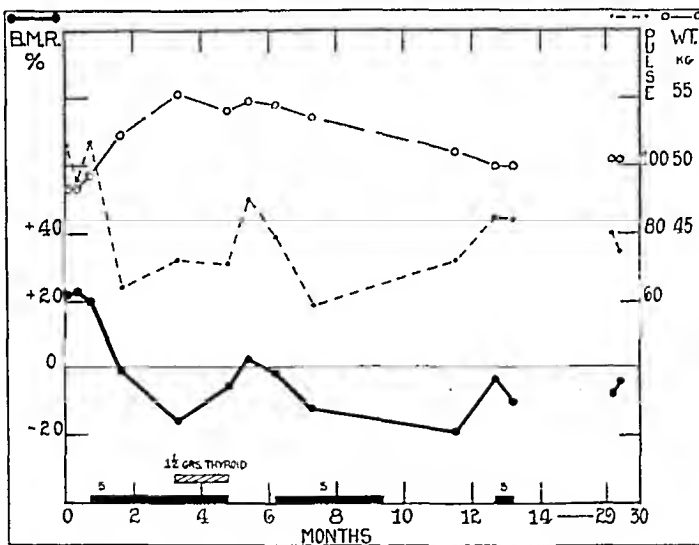


Chart 3 (case 3, lab. no. 4034).—In Miss F. K., a dentist's secretary, aged 17, mild exophthalmic goiter disappeared during prolonged iodine medication. At the time the first course of iodine was started: goiter ++, bruit ++, eyes staring, tremor 0, sweating +, nervousness ++, weight loss +. At the time of the last observation on the second course of iodine: goiter +, bruit 0, eyes slightly staring, tremor 0, sweating normal, nervousness +. The patient remained thus during the rest of the period of observation.

iodine medication were satisfactory in 37 per cent, fairly satisfactory in 17 per cent and unsatisfactory in 46 per cent.

Initial Severity of the Disease.—All nine patients (cases 1 to 9) who responded satisfactorily presented the disease in mild form. In all but one of the four patients (cases 10 to 13) who responded fairly satisfactorily the disease also occurred in a mild form: in case 13 the disease was moderately severe. In the group of eleven patients who did not respond satisfactorily, two had mild cases initially (cases 14

and 15), five moderately severe (cases 16, 18, 19, 20 and 21) and four severe (cases 17, 22, 23 and 24).

Thus in the fourteen mild cases, satisfactory results were obtained in 64 per cent, fairly satisfactory results in 22 per cent and unsatisfactory results in 14 per cent, in contrast to the ten severe and moderately severe cases in which there were no satisfactory results, fairly satisfactory results in only 10 per cent (one case), no permanent satisfactory benefit in 40 per cent and aggravation of symptoms in 50 per cent.

Miscellaneous Factors.—The data on the relation of the age of the patient, the duration of the disease, the consistency and size of the goiter and the presence of a bruit to the type of response to iodine are not extensive enough to warrant definite statements. As far as

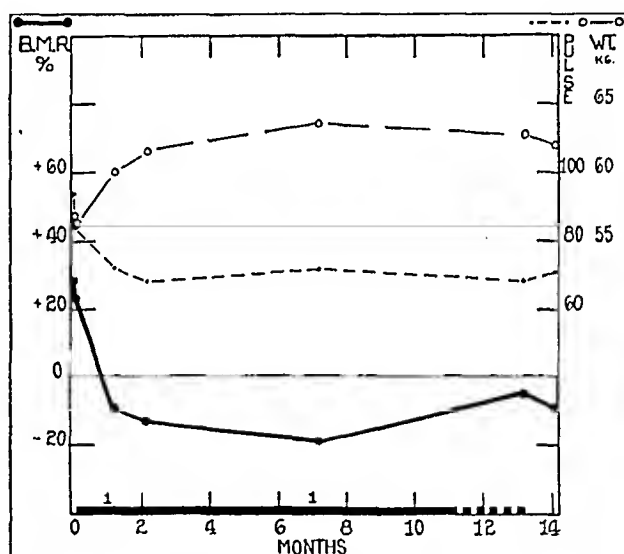


Chart 4 (case 5, lab. no. 5663).—In Mr. E. D., an x-ray technician, aged 49, control of and apparent disappearance of mild exophthalmic goiter were secured during prolonged iodine medication. At the time iodine was started: goiter +, bruit 0, exophthalmos +, tremor ++, sweating +, nervousness ++, weight loss ++. At the time of the last observation on iodine: goiter 0, bruit 0, exophthalmos less, tremor 0, sweating normal, nervousness 0. Following the omission of iodine, symptoms did not recur.

they go, they do not show that any of these factors has an important bearing on the results of prolonged iodine medication. There is a suggestion that the larger and firmer the thyroid gland, the less satisfactory the outcome with such treatment.

COMMENT

It is of interest to compare our results with prolonged iodine treatment in this series with those noted in similarly treating a group of patients who had thyrotoxicosis following a "subtotal" thyroidectomy

for exophthalmic goiter.²⁰ In ten of thirty-seven such patients its use was not continued long enough to determine the response. Eleven of the remaining twenty-seven patients, with basal metabolisms ranging from plus 20 to plus 45 per cent after operation, showed a satisfactory response to prolonged iodine medication; eight showed a fair response, and eight a poor response. In six of the eight patients who showed a poor response, a large amount of palpable thyroid tissue was noted and the disease was present in at least a moderately severe form. The group of eleven who responded well included ten with mild cases and one with a moderately severe case.

Thus our experiences with the postoperative group and with the group concerned in this paper have led us to believe that a certain number of patients with exophthalmic goiter can be satisfactorily

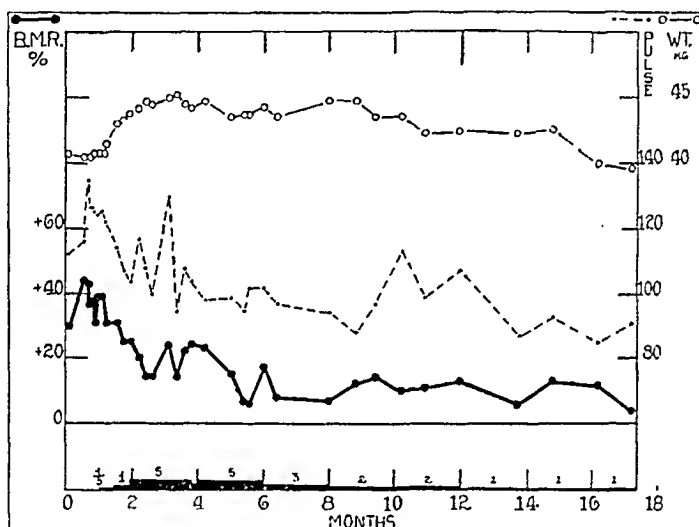


Chart 5 (case 8, lab. no. 5507).—In Miss M. C., a high school girl, aged 19, control of mild exophthalmic goiter was secured during prolonged continuous treatment with iodine alone. At the time iodine was started: goiter +, bruit +, exophthalmos 0, tremor 0, sweating +, nervousness +++, weight loss +. At the time of the last observation on iodine: goiter +, bruit 0, exophthalmos 0, tremor 0, sweating normal, nervousness +.

treated with iodine alone. At present there is no way of predicting definitely in any given case what the response to such treatment will be. Our data indicate that the single most important criterion may be the severity of the disease, mild cases usually doing well and severe or moderately severe cases usually showing no more than temporary improvement. The marked reduction in the intensity of the disease as a result of operation would appear to explain the large number of

20. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, to be published.

satisfactory results from this treatment in patients who have thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter.

Nevertheless, the severity of the disease at any given time is not the only consideration, as shown by the fact that even mild cases may occasionally become worse, and in a few instances a moderately severe case may do well during prolonged iodine administration. Inasmuch as the severity of the disease may vary markedly in the same patient from time to time, it is reasonable to suppose that the manner in which the disease is progressing spontaneously is important in determining the response. For example, it may be: (1) decreasing in severity and in a mild state when iodine medication is started; (2) increasing in severity from a mild to a more severe state before treatment with iodine is started, or (3) mild throughout its course, whether stationary or fluctuating in severity from time to time. Unfortunately,

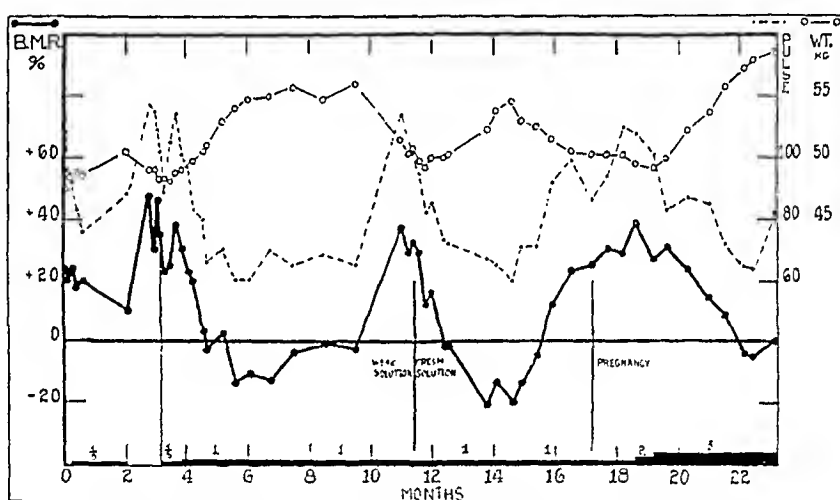


Chart 6 (case 10, lab. no. 5004).—In Mrs. M. P. W., a housewife, aged 20, there were three remissions and two mild relapses of mild exophthalmic goiter during continuous prolonged administration of iodine (preceded by a mild relapse on omission of the first course of iodine). The first relapse during the administration of iodine was possibly caused by weakening of the medicine. The second relapse on iodine was of unknown origin, but the disease may have been aggravated by the general malaise of the first few months of pregnancy. Improvement was coincident with the disappearance of nausea and vomiting. At the time the first course of iodine was started: goiter ++, bruit ++, exophthalmos +, (?) slight tremor, sweating +, nervousness ++, weight loss +. At the time of the last observation on iodine: goiter +, bruit 0, exophthalmos +, tremor 0, sweating normal, nervousness 0.

information of this type is rarely available, owing to the usual lack of time necessary for such observation before iodine medication is started. It is our impression that most of the patients in whom satisfactory or fairly satisfactory results were noted belong in groups 1 and 3.

The hypothesis that the natural course of the disease, i. e., whether fluctuating or stationary, and the intensity with which it is acting are important factors in determining the nature of the response to prolonged iodine medication is upheld by the observations on the following three cases:

Case 1 (chart 1) illustrates clearly an instance in which the natural course of the disease was the important factor in recovery. There had been a gradual spontaneous clinical improvement, accompanied by a drop in basal metabolism from plus 53 per cent to plus 27 per cent and a gain in weight from 49 to 56 Kg. for about six months before the seven months' course of iodine was started; but the disease apparently did not disappear completely until about five months after iodine was omitted. During the subsequent two years the patient presented no evidence of recurrence of thyrotoxicosis. Thus, in this case, iodine

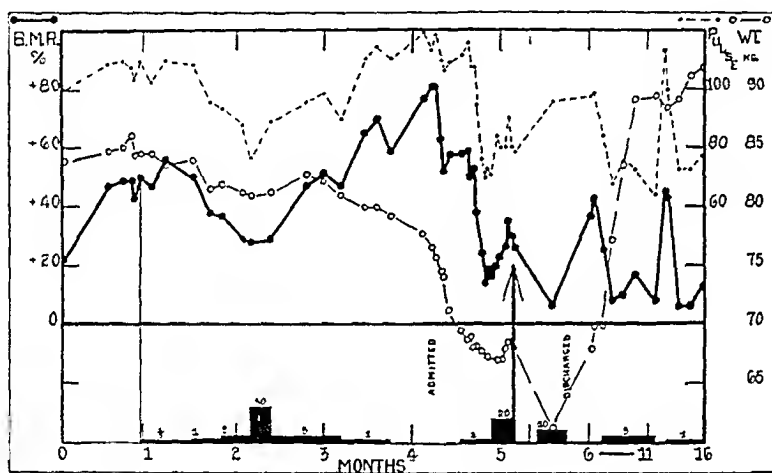


Chart 7 (case 18, lab. no. 5168).—In Mrs. E. H., a housewife, aged 26 years, slight improvement followed by an increase in severity of moderately severe exophthalmic goiter was noted during the continuous administration of iodine (first course). A further increase in severity occurred on omission of iodine with subsequent typical remission during administration of 1 drop of compound solution of iodine daily, just preceding subtotal thyroidectomy (arrow). Note that the disease was increasing in severity before treatment with iodine was started. At the time the first course of iodine was started: goiter ++, bruit ++, exophthalmos 0, tremor 0, sweating +, nervousness +, weight loss +++. At the time of the last observation on the first course of iodine: goiter ++, bruit +, exophthalmos +, tremor +, sweating +, nervousness ++.

can be credited only with holding the disease in check during the course of natural recovery. Complete recovery took place within three years after the onset of the disease (which was from one to two years before the patient was first seen in this clinic). Whether this was hastened or delayed by iodine is unknown.

In striking contrast to case 1 is case 18 (chart 7). As may be judged from the chart, the disease spontaneously changed from mild

to moderate severity in association with an increase in basal metabolism from about plus 22 per cent to about plus 50 per cent before treatment with iodine was begun. While iodine was still being administered, the patient, after showing an initial improvement, became slightly worse than before it was started, and when it was omitted, a little worse still. Thus, when the disease appeared to be getting worse spontaneously, iodine checked the increase in severity only temporarily.

In case 10 (chart 6) there were two relapses followed by remissions during the continuous administration of small doses of compound solution of iodine. At the time of the first relapse it was noted that the compound solution of iodine had become weaker.²¹ The patient was taking only one drop daily (about 6 mg. of iodine); we have observed that this is about the minimum dose that will produce a maximum

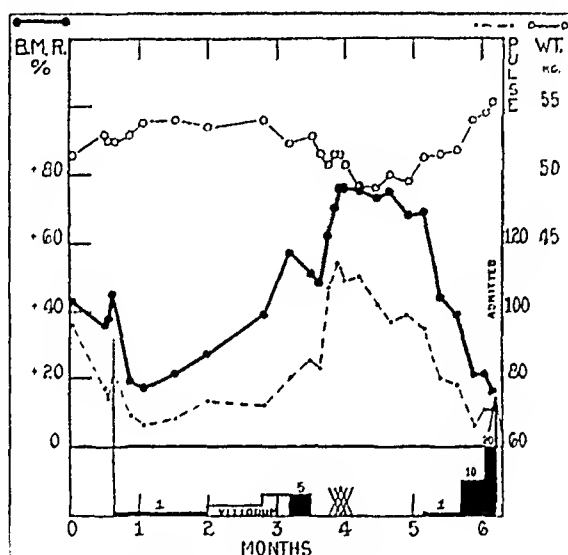


Chart 8 (case 19, lab. no. 6414).—In Mrs. E. R., a housewife, aged 34, during the continuous administration of iodine (first course) a remission was followed by an increase in the severity of exophthalmic goiter which was initially moderately severe. A further increase in severity occurred on omission of iodine. There was very slight clinical improvement from roentgen treatment (X) within one month. Iodine then produced a typical remission just preceding subtotal thyroidectomy (arrow). At the time that the first course of iodine was started: goiter +, bruit +, exophthalmos ++, tremor +, sweating +, nervousness ++, weight loss ++. At the time of the last observation on the first course of iodine: goiter ++, bruit ++, exophthalmos ++, tremor +, sweating ++, nervousness +++.

21. At the time the compound solution of iodine was noted to be weak, it was being kept in a cork-stoppered bottle. Under these circumstances a reaction takes place between the cork and the solution, as a result of which the cork is slowly destroyed and the solution becomes much paler. This does not occur if the solution is kept in a glass-stoppered bottle. This case has been reported in detail from the standpoint of the low metabolism in a paper by Thompson, Thompson, Brailey and Cohen, see footnote 22.

22. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Myxedema During the Administration of Iodine in Exophthalmic Goiter, *Am. J. M. Sc.*, to be published.

reduction in basal metabolism in most cases of exophthalmic goiter in Boston.²³ Shortly after the same dose of fresh solution was substituted, the basal metabolism began to drop. An inadequate intake of iodine may therefore well account for the first relapse during this medication. The second relapse, however, would appear to have a different explanation. Thyrotoxicosis had gradually recurred about one month before the patient became pregnant. This time the solution of iodine had lost only slightly in strength and the substitution of fresh solution was without effect. Similarly, tripling the dose of the fresh solution (three drops daily) did no good. Some degree of general malaise may have been the cause of the aggravation of symptoms observed

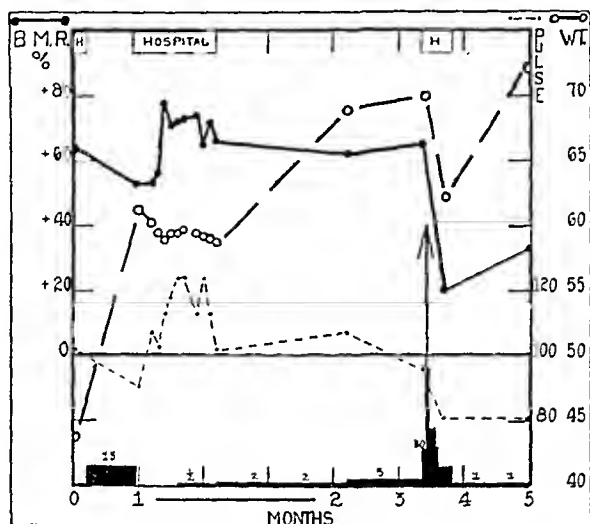


Chart 9 (case 22, lab. no. 6102).—Mr. J. C., a gardener-caretaker, aged 40, showed no significant drop in basal metabolic rate, yet a marked gain in weight and some clinical improvement in severe exophthalmic goiter during prolonged administration of iodine. At the time that the first course of iodine was started: goiter +, bruit ++, exophthalmos +, tremor ++, sweating ++, nervousness +++, weight loss +++. At the time of the last observation on the second course of iodine, that is, shortly before subtotal thyroidectomy (arrow): goiter ++, bruit 0, exophthalmos ++, tremor 0, sweating +, nervousness ++.

23. Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exophthalmic Goiter, *J. A. M. A.* **91**:1719 (Dec. 1) 1928. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, *Arch. Int. Med.*, in press. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, *Arch. Int. Med.*, in press. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, *Arch. Int. Med.*, in press.

for the first three months of pregnancy, during which time she had morning nausea and vomiting. As her general condition improved, her metabolism fell to normal and her thyroid gland became a little smaller and softer. The first relapse on iodine lasted from one to two months, and the second one, five months. It is of interest that at no time during either relapse did the basal metabolism go quite as high as it previously had when iodine was omitted. Presumably, a portion of the thyrotoxicosis was being held in check in spite of the relapse. During all three relapses (one without and two with iodine medication) the thyrotoxicosis was only mild, and it seems probable that in this

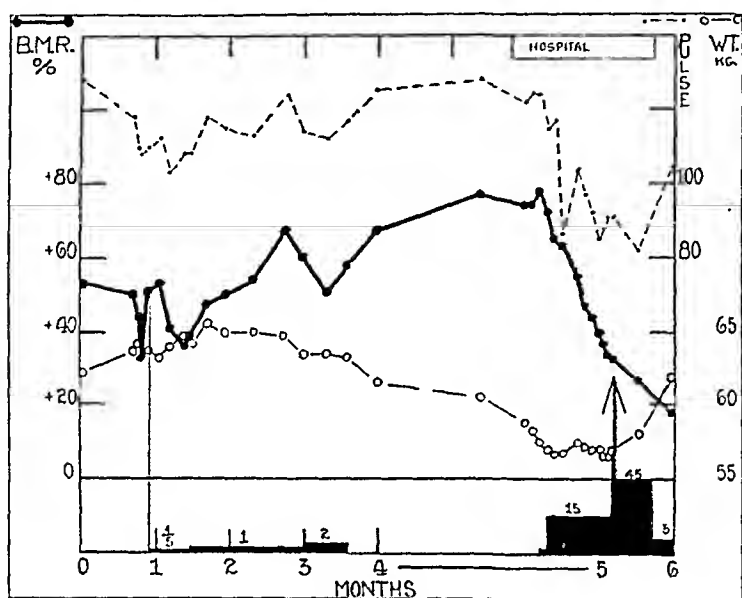


Chart 10 (case 24, lab. no. 5181).—Miss M. K., an office worker, aged 23, showed an increase in the severity of severe exophthalmic goiter, without any initial improvement, during the prolonged administration of iodine, and further increase in severity on omission of iodine. A subsequent typical remission occurred during the administration of iodine just before subtotal thyroidectomy (arrow). At the time that iodine medication was started: goiter ++, bruit ++, exophthalmos +, tremor ++, sweating +++, nervousness ++, weight loss ++. At the time of the last observation on the first course of iodine: goiter ++, bruit +, exophthalmos +, tremor +++, sweating +++, nervousness +++.

patient the disease may be held satisfactorily in check by iodine until it terminates.

Thus there are cases in which iodine does not appear to interfere with either the disappearance of the disease or an increase in its severity, and cases which show a spontaneous relapse followed by a remission during the continuous administration of iodine. In short, the response of patients with exophthalmic goiter to iodine appears to be determined not by the iodine, but by what is happening to the disease itself. The theory that iodine acts more as a check on the effects of the disease rather than as the remover of its cause has been

advanced in previous communications from this clinic.²⁴ While the bulk of the present data is consistent with such a view, the possibility remains that in cases in which the disease is acting with great intensity, iodine may sometimes aid the aggravation of symptoms by furnishing in excess one of the raw materials out of which a still greater amount of thyroxin may be made. This may be the explanation of the fact that five of our patients became worse during the administration of iodine although in them, as well as in the patients with mild cases who did well during this treatment, the natural course of the disease must be considered. In two patients (case 23 in table; case 24, chart 10) there was no improvement at any time, but a gradual increase in the severity of the signs and symptoms. This could be attributed to a natural increase in the severity of the thyrotoxicosis, over which iodine did not have even its usual temporary control. In three cases (case 17, table; case 18, chart 7; case 19, table) there was temporary improvement, but as the effect of iodine wore off, the patients were worse than before it was started. This, too, could be attributed to a natural increase in the severity of the disease, which iodine was finally unable to control. The increases in intensity were so marked and abrupt, however, that it seems possible that iodine may at least have been a factor in their production. There is much in the literature to the effect that prolonged iodine medication may aggravate the disease. If one may judge by the quantity of the reports and the acknowledged acumen of many of the authors, there must be some truth in the statement. However, the lack of a good control series of untreated cases is a serious obstacle to accepting this impression for fact.

It is hard to understand why in mild cases improvement will often continue as long as iodine is administered, whereas in severe cases it is usually only temporary and a stage is reached in which the disease may be worse than before iodine was started and the portion of the thyrotoxicosis still controlled by iodine smaller than initially. Indeed one of the patients in this series (case 17 in table) became completely refractory to one drop of compound solution of iodine daily during the continuous administration of iodine, and after a short period of freedom from iodine, showed a marked reduction in basal metabolism on this dose. It would seem that if the disease is acting with great intensity it can at least partially overcome the beneficial effect of iodine, whereas if it is acting only with mild intensity it cannot.

24. Means, J. H.; Thompson, W. O., and Thompson, P. K.: On the Nature of the Iodine Reaction in Exophthalmic Goiter: With Particular Reference to the Effect of Iodine Late in the Course of the Disease, *Tr. A. Am. Phys.* **43**:146, 1928. Means, J. H., and Richardson, E. P.: *The Diagnosis and Treatment of Diseases of the Thyroid*, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 151.

The percentage of unselected cases of exophthalmic goiter that will show a satisfactory response to prolonged iodine medication is unknown, but is probably small. We wish to emphasize that the results in our series do not represent the results to be expected in an unselected group, inasmuch as the majority were selected because they had the disease in mild form. There would appear to be little virtue in trying to treat patients with moderately severe or severe forms of the disease in this manner. If the effect of this treatment were to be judged by the response in an unselected group of cases, without reference to the severity of the disease, the results usually would be so poor that prolonged iodine medication would be regarded as too dangerous a method of treatment to employ in any type of case. By limiting this treatment to mild cases, however, a high percentage of satisfactory results probably would be secured and little damage done. It is perhaps needless to add that patients should be examined and have their basal metabolisms determined about once a month throughout the period of observation. Moreover, before treatment is begun, patients should be told that its results are uncertain and that an operation eventually may be necessary.

What effect iodine has on the duration of the disease in the cases responding satisfactorily is unknown. To determine this, it is necessary to have accurate statistics regarding the course of the disease in untreated patients. Unfortunately, none are available. Hyman and Kessel's²⁵ series of patients, while purporting to show the "spontaneous course," was treated mainly by rest and also by iodine. Hale-White's²⁶ and Campbell's²⁷ patients were treated by rest and also in some instances by "galvanism" or by roentgen rays. From isolated observations, however, it is known that in a certain number of cases of exophthalmic goiter the disease will disappear without treatment in the course of a few years.

In the four cases in which the disease came to an end (cases 1, 2 and 3, charts 1, 2 and 3; case 4 in table), iodine may have acted in any of three ways:

1. It may have merely held the disease in check until a spontaneous recovery took place, which was not hastened by this treatment.
2. While holding the disease in check, it may have hastened spontaneous recovery.

25. Hyman, H. T., and Kessel, L.: Studies of Exophthalmic Goiter and the Involuntary Nervous System: X. The Course of the Subjective and Objective Manifestations in Fifty Unselected Patients Observed Over a Period of Two Years, in Whom no Specific Therapeutic Measures Were Instituted ("Spontaneous Course"), *Arch. Surg.* 8:149 (Jan.) 1924.

26. Hale-White, W.: The Outlook of Sufferers from Exophthalmic Goitre, *Quart. J. Med.* 4:89, 1910.

27. Campbell, J. M. H.: Some Aspects of Exophthalmic Goitre, *Quart. J. Med.* 15:55, 1921-1922.

3. It may have instigated a recovery which otherwise would not have taken place.

In the remaining cases showing a satisfactory response, iodine has not been omitted for a sufficient length of time to draw conclusions as to whether the disease is retrogressing or has disappeared. All that can be said is that iodine held the symptoms efficiently in check for long periods, usually for more than a year (cases 5 and 8, charts 4 and 5; cases 6, 7 and 9 in table). Aside from this, what influence it has had on the course of the disease in the meantime is a matter of conjecture.

While iodine may have more far-reaching effects in mild exophthalmic goiter, even the fact that it usually produces an abrupt remission and at least holds the disease in check while it is pursuing its natural course, makes it a valuable method of treatment in this type of case.

The usual striking effect of rest in bed emphasizes the importance of eliminating this factor when judging the effect of iodine alone in the treatment for exophthalmic goiter. For this reason we wish to stress the fact that ours was essentially an outpatient series. There were three exceptions (cases 15 and 21 in table; case 22, chart 9). Iodine medication was started on discharge of the patient from the hospital. Thus the change from rest to activity may have been a factor in the unsatisfactory response to iodine. Recovery or remission in all the cases showing satisfactory results took place during the stress of the patient's customary routine. For example, patient 8 (chart 5), a naturally high-strung girl, continued her junior and senior high school work during the period of observation. Previous to treatment she had taken part in a play and had broken down completely in the first act. After she had been given iodine continuously for about a year, she took a leading part in another play. She acted her part well and did not suffer from undue nervousness either during rehearsals or in the actual performances. During treatment, patients 5 (chart 4), 11 and 13 (table) continued their occupations of x-ray technician, stenographer and gardener, respectively. In patient 6 (table) the control of signs and symptoms of thyrotoxicosis, including the disappearance of auricular fibrillation, was maintained in spite of the emotional strain resulting from life with a rather worthless husband, and in spite of a major pelvic operation. The other patients had the usual amount of housework to perform.

Some observers are of the opinion that small doses are less liable to do harm during prolonged medication than are large doses.²⁸ While

28. Beebe (footnote 8). Cowell and Mellanby (footnote 11). Fraser (footnote 14). Cole (footnote 18). Marine, D.: *Iodin in the Treatment of Diseases of the Thyroid Gland*, Medicine 6:127, 1927.

in our series the customary dose has been comparatively small, i. e., one drop of compound solution of iodine (about 6 mg. of iodine) daily, in instances in which it was administered for a time in much larger doses, even as much as ninety drops daily (case 17, table), there was no proof that the increase had an aggravating effect. Patient 16 (table), while not receiving any more than one drop daily, after striking temporary improvement had a relapse on this dose. The data suggest that the response to iodine in exophthalmic goiter is determined not by the size of the dose, as long as it is large enough to produce a maximum effect, but by something fundamental about the disease, presumably related to its cause, over which iodine exercises no control. Undoubtedly small doses are more palatable than large doses. For this reason, during prolonged medication, we generally use approximately the smallest dose which will produce a maximum effect on basal metabolism. In Boston, this appears to be about one drop of compound solution of iodine daily.²³

SUMMARY

Twenty-four patients with exophthalmic goiter (fourteen mild and ten severe or moderately severe cases) have been treated in this clinic with iodine alone, either continuously or intermittently for periods ranging from one and one-half months to three years. The period of treatment was a year or more in thirteen instances.

With three exceptions (all unsatisfactory responses to iodine) the patients pursued their daily work throughout the period of observation, thus eliminating the effect of rest.

In nine of the fourteen mild cases (64 per cent) the results were satisfactory; i. e., the clinical evidence of thyrotoxicosis was either completely or almost entirely kept under control, and the basal metabolism was kept at a normal level. In four of these nine cases (in which iodine was omitted from ten to sixteen months) the disease has apparently disappeared, and in three others in which it has been omitted from four to seventeen weeks, there has been no recurrence of symptoms. In three of the fourteen mild cases (22 per cent) the results were fairly satisfactory; i. e., there was definite improvement in spite of tardiness or fluctuations in the response. In two mild cases (14 per cent) the results were unsatisfactory; the disease did not become worse, however, on iodine.

In the ten severe or moderately severe cases, the results were satisfactory in one (10 per cent); there was no permanent satisfactory benefit in four (40 per cent), and the disease became worse in five (50 per cent).

CONCLUSIONS

Patients with moderately severe or severe exophthalmic goiter rarely show more than temporary improvement during the prolonged administration of iodine. Frequently the disease becomes more severe than before iodine was started.

If the disease is mild, however, the patients often respond satisfactorily, and in some patients it terminates. The proportion of unsatisfactory results in Boston appears to be so small that it is not a contraindication to prolonged treatment with iodine if strictly confined to mild cases and if the patients are kept under close observation.

The response of patients with exophthalmic goiter to prolonged iodine medication appears to be determined more by what is happening to the disease spontaneously than by the iodine itself. In the cases showing satisfactory results, iodine may have merely held the disease in check while it was pursuing its natural course. Even this, however, makes it valuable in the treatment for mild exophthalmic goiter.

THE SIZE OF THE HEART IN EXPERIMENTAL HYPERTHYROIDISM *

J. P. SIMONDS, M.D.

AND

W. W. BRANDES, M.D.

CHICAGO

Accurate data concerning the effect of hyperthyroidism on the size of the heart do not appear to be available in the literature. Not only is the heart rate markedly increased in this condition but, according to Samson Wright,¹ the stroke volume in exophthalmic goiter averaged 116 cc., as compared with the normal of from 70 to 120 cc. at rest; the minute output averaged 11.7 liters as compared with from 5 to 8 liters in normal persons at rest. The increased output of the heart may not be due to the tachycardia per se, for Stewart and Crawford² induced regular tachycardias by means of single induced break shocks thrown into the auricle at a regular rapid rate of between 250 and 400 per minute, and found that the blood flow was usually unchanged and in one third of the observations it was decreased.

Observations on the size of the heart in hyperthyroidism are difficult to obtain. Chvostek³ stated that "only in severe cases of exophthalmic goiter is there hypertrophy of the heart." According to Bickel,⁴ the pathologic anatomy of the heart in exophthalmic goiter consists essentially in an increase of the volume of the organ. Willius and Boothby⁵ observed that the hearts of most patients with exophthalmic goiter or adenomatous goiter with hyperthyroidism were only moderately enlarged. In their series of cases the blood pressure was 147 systolic and 73 diastolic with a pulse rate of 123, and 153 systolic and 83 diastolic with a pulse rate of 110 in exophthalmic goiter and adenomatous goiter, respectively. Wilson⁶ asserted that in hyperthy-

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* From the Department of Pathology of Northwestern University Medical School.

1. Wright, Samson: *Applied Physiology*, London, Oxford University Press, 1926, p. 128.

2. Stewart, H. J., and Crawford, J. H.: *J. Clin. Investigation* **3**:449, 1926.

3. Chvostek, F.: *Wien. klin. Wchnschr.* **30**:383 and 643, 1917.

4. Bickel, G.: *Schweiz. med. Wchnschr.* **11**:251, 1926.

5. Willius, F. A., and Boothby, W. M.: *M. Clin. North America* **7**:189, 1923.

6. Wilson, F. N.: *Cardiac Disturbances Associated with Diseases of the Thyroid Gland*, J. A. M. A. **82**:1754 (May 31) 1924.

roidism "we find enlargement of the heart." Symmers⁷ reported six cases of idiopathic cardiopathy—enlargement of the heart due to dilatation and hypertrophy of all of the chambers or of different combinations of the chambers—without valvular, pericardial, arterial, renal, pulmonary or other causes customarily invoked to explain enlargement of the heart. In all of these cases the thyroid showed chronic interstitial and hyperplastic thyroiditis.

The experimental work on this subject recorded in the literature appears to have been limited to rats and rabbits. Iscovesco⁸ gave daily injections of thyroid extract and observed loss of body weight in old animals, together with hypertrophy of the various viscera. Hoskins,⁹ working with white rats, observed "marked hypertrophy of the heart." He estimated that this increase in heart weight amounted to 24.6 and 16.7 per cent, respectively, in old and young female rats, and to 36 and 15.4 per cent, respectively, in corresponding males. Hewitt¹⁰ found that the administration of 0.1 Gm. or more of fresh thyroid daily to adult male white rats caused hypertrophy of the heart. We have been unable to find in the literature any reference to the effect of thyroid feeding on the size of the heart in dogs. Cameron and Carmichael¹¹ fed thyroid preparations to young rats and rabbits and produced hypertrophy of the heart.

EXPERIMENTAL WORK

The experiments herein reported are concerned with eleven dogs, to ten of which 10 Gm. of desiccated thyroid (Armour and Company) was fed daily, and to the other dog, 20 Gm., for periods varying from thirty-two to one hundred days. In all of these animals the final body weight was recorded (designated as F.B.W. in the tables), and in ten, the original body weight was also recorded (designated as O.B.W. in the tables). After the animal had been killed the heart was carefully denuded of fat and weighed. It was then dissected according to Mueller's method,¹² and the auricles (designated as Au.W.), the ventricles and septum combined (designated as V.W.), the right ventricle (designated as R.V.W.), the left ventricle (designated as L.V.W.) and the septum were each weighed separately, and their respective

7. Symmers, D.: Cardiopathy and Goiter, *Arch. Int. Med.* **21**:337 (March) 1918.

8. Iscovesco, H.: *Compt. rend. Soc. de biol.* **76**:75, 1914.

9. Hoskins, E. R.: *J. Exper. Zool.* **21**:295, 1916.

10. Hewitt, J. A.: *Quart. J. Exper. Physiol.* **12**:347, 1918-1920.

11. Cameron, A. T., and Carmichael, J.: *J. Biol. Chem.* **45**:69, 1920; *Tr. Roy. Soc., Canada* **16**:57, 1922; *ibid.* **18**:105, 1924.

12. Mueller: *Die Massenverhältnisse des menschlichen Herzens*, Braunschweig and Leipzig, 1883; cited by Hasenfeld: *Deutsches Arch. f. klin. Med.* **59**:193, 1897.

weights were recorded. Body weights and corresponding heart weights were recorded for thirty-one normal dogs kept under similar conditions and fed on the same diet as those to which desiccated thyroid was administered. In addition, records of body weights and whole heart weights have been collected from the literature in cases of experiments on inanition in dogs.¹³ For comparison, the studies on changes in heart weights in animals in which aortic regurgitation had been induced by Stewart¹⁴ and by Herrmann¹⁵ were analyzed. The following ratios, with their designations in the tables, were analyzed and compared with corresponding ratios in inanition and aortic regurgitation:

H.W./N.B.W. = heart weight-body weight ratio in normal dogs.

H.W./O.B.W. = heart weight-original body weight ratio in thyrotoxic and starved dogs.

H.W./F.B.W. = heart weight-final body weight ratio in thyrotoxic and starved dogs.

L.V.W./N.B.W. = left ventricle weight-body weight ratio in normal dogs.

L.V.W./O.B.W. = left ventricle weight-original body weight ratio in thyrotoxic and aortic regurgitation dogs.

L.V.W./F.B.W. = left ventricle weight-final body weight ratio in thyrotoxic and aortic regurgitation dogs.

R.V.W./N.B.W.

R.V.W./O.B.W. = corresponding ratios for the right ventricle.

R.V.W./F.B.W.

Au.W./N.B.W.

Au.W./O.B.W. = corresponding ratios for the auricles.

Au.W./F.B.W.

V.W./N.B.W.

V.W./O.B.W. = corresponding ratios for the ventricles and septum.

V.W./F.B.W.

In table 1 it is seen that the mean heart weight-original body weight ratio of the thyrotoxic dogs was only 0.00058, while that of the starved dogs was 0.00171, less than the corresponding ratio for normal dogs. The mean heart weight-final body weight ratio for thyrotoxic dogs was 0.00232 greater, and that of the starved dogs 0.00059 greater, than the mean ratio of normal dogs. These figures become more significant when it is observed from table 1 that the mean loss of body weight in the thyrotoxic dogs was 31 and for the starved dogs 28.1 per cent. It is to be observed further that the mean losses of

13. Junkersdorf, P.: *Arch. f. d. ges. Physiol.* **200**:443, 1923. Witsch, Käthe: *Arch. f. d. ges. Physiol.* **211**:185, 1926. Junkersdorf, P., and Török, P.: *Arch. f. d. ges. Physiol.* **211**:414, 1926. Junkersdorf, P., and Kohl, A.: *Arch. f. d. ges. Physiol.* **211**:612, 1926.

14. Stewart, H. A.: *J. Exper. Med.* **13**:187, 1911.

15. Herrmann, G. R.: *Am. Heart J.* **1**:213 and 485, 1925-1926.

body weight in these two series of animals were almost the same—a difference of only 2.9 per cent—although the mean heart weight-body weight ratios were much lower in inanition.

In table 2, which is based on the figures in table 1, are shown the percentage differences between mean, minimum and maximum ratios in normal and in thyrotoxic and starved dogs. The figures for the latter group have been taken from papers published from Junkersdorf's

TABLE 1.—*The Mean Minimum and Maximum Heart Weight-Body Weight Ratios for Normal, Thyrotoxic and Starved Dogs*

Condition	Ratio	Mean	Minimum	Maximum	Mean Loss of Body Weight, Per Cent
Normal, own series	H.W./B.W.	0.00758	0.00560	0.00980	
	Stewart H.W./B.W.	0.00724	0.00599	0.00856	
	Herrmann H.W./B.W.	0.00798	0.00600	0.00994	
Thyrotoxicosis	H.W./O.B.W.	0.00700	0.00450	0.00825	
	H.W./F.B.W.	0.00990	0.00820	0.01190	—31.0
Inanition	H.W./O.B.W.	0.00587	0.00430	0.00708	
	H.W./F.B.W.	0.00817	0.00650	0.00900	—28.1

TABLE 2.—*The Percentage Difference Between Various Ratios in Normal, Thyrotoxic and Starved Dogs with the Corresponding Losses of Body Weight in the Latter Groups*

Ratios Compared	Thyrotoxicosis		Inanition	
	Percentage Difference	Percentage Loss of Body Weight	Percentage Difference	Percentage Loss of Body Weight
Mean H.W./N.B.W.				
Mean H.W./O.B.W.	— 7.7	—31.0	—22.5	—28.1
Mean H.W./N.B.W.				
Mean H.W./F.B.W.	+31.6	—31.0	+ 7.8	—28.1
Min. H.W./N.B.W.				
Min. H.W./O.B.W.	—18.6	—46.5	—23.3	—50.2
Min. H.W./N.B.W.				
Min. H.W./F.B.W.	+46.4	—46.5	+16.1	19.1
Max. H.W./N.B.W.				
Max. H.W./O.B.W.	—15.8	—30.4	—27.8	—20.7
Max. H.W./N.B.W.				
Max. H.W./F.B.W.	+21.4	—30.4	— 8.2	—43.5

laboratory.¹³ In the column "percentage difference" in table 2, the figures indicate the degree to which the second ratio in each pair is greater or less than the first ratio in each pair. From this table three facts appear to be evident: 1. The mean, minimum and maximum heart weight-final body weight ratios in thyrotoxic dogs not only were much greater than the corresponding ratios in normal dogs, but were also considerably greater than the corresponding ratios in the starved animals. 2. The mean, minimum and maximum heart weight-original body weight ratios for thyrotoxic dogs were less than the corresponding ratios for normal dogs, but the difference was considerably less than

in the case of the starved dogs. 3. The minimum heart weight-original body weight and heart weight-final body weight ratios were found in the same animal of the thyrotoxic series, but in different dogs in the inanition series. The same applies to the maximum heart weight-original body weight and heart weight-final body weight ratios.

Using the normal ratio of 0.00758, the heart weight that would have been normal for the final body weight of each thyrotoxic dog was calculated. This figure was compared with the actual heart weight of the animal. In each instance the actual weight exceeded the calculated weight. It is seen from table 3 that if the figures in the last column were plotted as ordinates and the percentage loss of body weight as abscissae the curve would be remarkably regular. The maximum difference was in the animal that had lost 30.4 per cent of its body weight.

TABLE 3.—*The Percentage Difference Between the Actual Heart Weight and the Calculated Heart Weight for the Final Body Weight in Thyroid-Fed Dogs*

Dog No.	Days of Thyroid Feeding	Original Body Weight, Kg.	Final Body Weight, Kg.	Percentage Loss of Body Weight	Actual Heart Weight, Gm.	Calculated Heart Weight for Final Body Weight, Gm.	Percentage Difference Between Actual and Calculated Heart Weight
1	48	11.9	10.2	14.3	85.0	77.5	+ 8.85
2	49	14.5	11.35	21.7	95.0	86.0	+ 9.80
3	57	11.6	8.8	24.2	92.0	67.0	+27.0
4	93	14.6	10.25	29.8	110.5	77.5	+30.0
5	82	9.7	6.75	30.4	80.0	52.3	+35.0
6	32	11.9	8.04	33.5	89.0	61.0	+31.5
7	70	9.2	5.9	35.8	63.0	45.0	+28.5
8	57	10.5	6.7	36.1	71.0	51.0	+28.0
9	91	15.85	9.65	39.2	84.0	73.0	+13.0
10	100	13.9	7.39	46.5	60.5	56.0	+ 7.5
Mean percentage difference = + 21.							

The highest part of the curve corresponds to the zone of from approximately 25 to 35 per cent loss of body weight. The difference between the actual and the calculated heart weights appears to be more directly related to the loss of body weight than to the length of time thyroid was fed to the animal.

Similar calculations were made for the heart weight that would have been normal for animals of the final body weight in a series of reports on inanition from Junkersdorf's laboratory,¹³ and these were compared with the actual heart weights of the same animals. The percentage difference between the actual and the calculated heart weights in this series ranged from -16.3 in a dog that had lost 29.5 per cent of its body weight, to maxima of +15.5 in a dog that had lost 20.7 per cent and +15.8 in one that had lost 43.5 per cent. It is evident, therefore, that this percentage difference in the starved dogs has no such definite relation to the loss of body weight as in the thyrotoxic series. The mean percentage difference was more than four times as

great in the thyrotoxic dogs as in the starved animals—+ 21 and + 5, respectively.

It would appear from the foregoing data that an apparent increase in heart weight of from a mean value of approximately 5 to a maximum of approximately 16 per cent may be accounted for by the fact that the heart does not lose weight to the same extent as the body as a whole. Any such increase greater than 16 per cent is probably due to an actual increase in the size of the heart. If this is correct, those thyrotoxic dogs that had lost from approximately 25 to approximately 35 per cent (actually from 24.2 to 36.1 per cent) showed an actual hypertrophy of the heart. In the most marked case, that of dog 5 with 30.4 per cent loss of body weight, the actual increase in heart weight was more than 25 per cent (35 per cent minus the mean difference of 5 per cent due to failure of the heart to lose weight as rapidly as the

TABLE 4.—*Ratios Between Actual Weights of Different Parts of the Heart and the Body Weight in Thyrotoxic and Normal Dogs*

Ratios	Thyrotoxicosis			Normals		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum
L.V.W./O.B.W.	0.00278	0.00218	0.00345	0.00293	0.00194	0.00392
L.V.W./F.B.W.	0.00415	0.00354	0.00465			
R.V.W./O.B.W.	0.00143	0.00072	0.00176	0.00161	0.00117	0.00237
R.V.W./F.B.W.	0.00215	0.00135	0.00306			
V.W./O.B.W.	0.00690	0.00383	0.00735	0.00654	0.00475	0.00852
V.W./F.B.W.	0.00880	0.00725	0.01065			
Au.W./O.B.W.	0.00077	0.00054	0.00105	0.00081	0.00055	0.00135
Au.W./F.B.W.	0.00112	0.00080	0.00159			
L.V.W./H.W.	0.4114	0.3450	0.5618	0.3891	0.3160	0.4380
R.V.W./H.W.	0.2125	0.1658	0.2432	0.2153	0.1640	0.2600
L.V.W./R.V.W.	2.15	1.54	3.40	2.03	1.48	2.57

body as a whole). With an increasing loss of body weight above 35 per cent the heart appears to lose what it has gained as a result of hypertrophy.

If the foregoing figures do indicate actual hypertrophy of the heart, it is important to determine whether the organ increases in size in all its parts or whether the hypertrophy is limited to one or more chambers. In table 4 are shown ratios between actual weights of different parts of the heart and the body weight in thyrotoxic and normal dogs.

From table 4 it appears that: 1. The mean, minimum and maximum ratios between the weights of various parts of the heart and the final body weight are considerably greater than the corresponding ratios in normal dogs. 2. The ratios between the weights of various parts of the heart and the original body weight are not nearly as great as the percentage loss of body weight and do not differ markedly from the corresponding normal ratios. This is shown to better advantage in table 5.

From table 5 it is seen that the mean, minimum and maximum left ventricle-final body weight ratios exceeded the corresponding normal ratios. The mean and maximum left ventricle-original body weight ratios were less than the normal but the difference was not as great as the loss of body weight. The minimum left ventricle-original body weight ratio was actually greater than the corresponding normal ratio. The mean right ventricle-final body weight ratio was one-third greater, and the right ventricle-original body weight ratio only one-eighth less, than the normal. The mean total ventricle and septum weight-final

TABLE 5.—*Percentage Difference Between Mean, Minimum and Maximum Ratios Between the Weights of Various Parts of the Heart and the Original and Final Body Weights*

Ratios Compared	Percentage Difference	Percentage Loss of Body Weight
L.V.W./N.B.W. Mean		
L.V.W./O.B.W. Mean	— 5.12	—31.0
L.V.W./N.B.W. Mean		
L.V.W./F.B.W. Mean	+41.64	—31.0
L.V.W./N.B.W. Min.		
L.V.W./O.B.W. Min.	+12.37	—39.2
L.V.W./N.B.W. Min.		
L.V.W./F.B.W. Min.	+46.00	—21.7
L.V.W./N.B.W. Max.		
L.V.W./O.B.W. Max.	—12.00	—24.2
L.V.W./N.B.W. Max.		
L.V.W./F.B.W. Max.	+18.62	—35.8
R.V.W./N.B.W. Mean		
R.V.W./O.B.W. Mean	—12.58	—31.0
R.V.W./N.B.W. Mean		
R.V.W./F.B.W. Mean	+33.60	—31.0
V.W./N.B.W. Mean		
V.W./O.B.W. Mean	— 9.0	—31.0
V.W./N.B.W. Mean		
V.W./F.B.W. Mean	+34.55	—31.0
Au.W./N.B.W. Mean		
Au.W./O.B.W. Mean	— 5.32	—31.0
Au.W./N.B.W. Mean		
Au.W./F.B.W. Mean	+38.27	—31.0

body weight and the mean auricle weight-final body weight ratios were approximately one-third greater than normal. The corresponding original body weight ratios were less than 10 per cent below the normal. These figures appear to indicate, therefore, that in the experiments here recorded feeding thyroid to dogs causes, especially in animals that have lost from 25 to 35 per cent of their body weight, an actual hypertrophy of the heart involving all of the chambers. This is brought out even more clearly when the figures in these thyrotoxic dogs are compared with corresponding figures obtained by Stewart and by Herrmann in experimental aortic regurgitation. This is shown in table 6.

Table 6 shows that the difference between the mean heart weight-final body weight ratio in thyrotoxic dogs and the heart weight-body

weight ratio in normal dogs is almost as great as in aortic regurgitation, while in inanition the difference is much less. The mean left ventricle-heart weight ratio in thyrotoxicosis is only slightly less than in aortic regurgitation. The mean right ventricle weight-heart weight ratio is markedly less (20.5 per cent) in aortic regurgitation and is only 1.33 per cent less in thyrotoxicosis than the normal ratio. The left ventricle weight-right ventricle weight ratio is greatly increased in aortic regurgitation and only slightly increased in thyrotoxicosis. These figures indicate that the increase in size of the heart in thyrotoxicosis involves all of the chambers in contrast to aortic regurgitation in which the hypertrophy is practically limited to the left ventricle. In this connection, it is interesting to note that electrocardiograms of these thyrotoxic dogs showed no ventricular preponderance.

TABLE 6.—*Comparison Between Various Heart Weight-Body Weight Ratios in Aortic Regurgitation, Thyrotoxicosis and Inanition*

Percentage Difference Between Mean	Aortic Regurgitation, Per Cent		Thyrotoxicosis, Per Cent	Inanition, Per Cent
	Stewart	Herrmann		
H.W./N.B.W.				
H.W./F.B.W.	+39.5	+31.95	+30.61	+11.87
L.V.W./N.H.W.				
L.V.W./H.W.	+ 9.66		+ 5.73	
R.V.W./N.H.W.				
R.V.W./H.W.	-20.50		- 1.33	
L.V.W./R.V.W. Normal				
L.V.W./R.V.W.	+41.97	+31.00	+ 5.90	

In order to determine whether there was any reciprocal relationship between body weights and heart weights, correlation coefficients were calculated in the case of our normal and thyrotoxic dogs. These have been compared with the coefficients published by Herrmann. From the data published in Stewart's paper we have determined correlation coefficients in his normal animals and those in which he had induced experimental aortic regurgitation. A similar calculation was made from data in papers from Junkersdorf's laboratory in the case of dogs that had been starved for varying intervals of time. A correlation coefficient of 1 indicates that there is a perfect reciprocal relation between the weights compared. From table 7 it is seen that there is a definite correlation between body weight and heart weight in normal animals. The coefficient of correlation between heart weight and final body weight in inanition was only slightly less than the average normal, which indicates that in this condition the heart loses weight in almost the same proportion as the body as a whole. In the case of the thyrotoxic dogs the coefficient was, in every instance, considerably less than

the normal, which is evidence that in experimental hyperthyroidism the heart does not lose weight to the same extent as the body. This furnishes further indication that in the animals used in these experiments an actual hypertrophy of the heart did occur. In all except one instance the correlation coefficients were higher in thyrotoxicosis than in aortic regurgitation. This is in harmony with facts presented in other tables in this paper and shows that the hypertrophy in experimental thyrotoxicosis is not as great as in aortic regurgitation.

The coefficient of correlation between heart weight and right and left ventricle weights, respectively, is not as perfect as one would

TABLE 7.—*Correlation Coefficients*

Variables Correlated		Correlation Coefficients			
		Normals	Thyrotoxi- cosis	Inanition	Aortic Regurgitation
H.W. and F.B.W.	Own series	0.9062	0.8206	0.9075*	0.7670
	Stewart	0.9490			
	Herrmann	0.9152			
	Average	0.9235			
L.V.W. and F.B.W.	Own series	0.8790	0.8360		0.6795
	Stewart	0.9490			
	Herrmann	0.9104			
	Average	0.9128			
R.V.W. and F.B.W.	Own series	0.8104	0.7090		0.6893
	Stewart	0.8770			
	Average	0.8437			
H.W. and L.V.W.	Own series	0.9730	0.8967		0.8010
	Stewart	0.8900			
	Average	0.9315			
H.W. and R.V.W.	Own series	0.9675	0.8570		0.9040
	Stewart	0.9124			
	Average	0.9399			
H.W. and Au.W.	Own series	0.9038	0.7220		0.7212
	Stewart	0.9632			
	Average	0.9320			
R.V.W. and L.V.W.	Own series	0.9200	0.7670		0.7600
	Stewart	0.8860			
	Herrmann	0.9688			
	Average	0.9239			

* Based on data published from Junkersdorf laboratory.

expect if all of the heart chambers were equally hypertrophied in thyrotoxicosis. In table 6 it was found that the mean left ventricle weight-right ventricle weight ratio was approximately 6 per cent greater than the corresponding normal ratio. The figures in table 4 show an almost identical difference. This suggests that the left ventricle was slightly more hypertrophied than the right. In order to determine this more accurately, the right and left ventricle weights that would have been normal for the heart weights in the thyrotoxic dogs and in Stewart's animals with aortic regurgitation were calculated (using the mean ratios 0.3891 and 0.2153 in table 4) and compared with the actual heart weights. It was found that the mean actual left ventricle weight in the thyrotoxic dogs was 6.9 per cent greater than the mean calculated weight, while the mean actual right ventricle weight was 2.25 per

cent less than the corresponding calculated weight. In Stewart's dogs with aortic regurgitation the actual left ventricle weight was 17.3 per cent greater, and the actual right ventricle 17.8 per cent less, than the corresponding calculated weights. These figures seem, therefore, to indicate that in experimental hyperthyroidism the heart hypertrophies as a whole with a slightly greater increase (approximately 6 per cent) in the left ventricle. This is in striking contrast to aortic regurgitation in which the left ventricle is markedly increased.

SUMMARY

1. Feeding 10 Gm. of desiccated thyroid daily to healthy dogs can cause an actual hypertrophy of the heart.
2. This hypertrophy is related to the loss of body weight, and occurs in those animals which have lost from approximately 25 to 35 per cent of their original body weight. When the loss of weight exceeds approximately 35 per cent, the heart loses the weight it has gained in hypertrophy and the heart weight-final body weight ratio approaches that seen in simple inanition.
3. This hypertrophy involves all of the chambers of the heart with a slightly greater proportional increase in the left ventricle.

BILATERAL ABSENCE OF PULSE IN THE ARMS AND NECK IN AORTIC ANEURYSM*

R. H. KAMPMEIER, M.D.

PUEBLO, COLO.

AND

V. F. NEUMANN, M.D.

DETROIT

The absence of pulsation in the radial, brachial and carotid arteries of both sides is a rare condition. A patient showing such abnormality was under observation in the wards of the University Hospital. In a study of the literature only three reports of instances in which this striking abnormality occurred were found. We are collecting and reviewing these, adding our report of a case as a fourth.

INCIDENCE

Because of the frequency of aortic aneurysm, large groups of statistics are available dealing with signs and symptoms in the presence of this lesion. Boyd¹ in 1924 studied collected reports on 4,000 cases of thoracic aortic aneurysm, stating that over 5,000 cases had been reported in the literature. Since we are dealing with a not uncommon lesion, the finding of only three reports of cases of bilateral absence of pulse indicates the extreme rarity of this remarkable abnormality.

Pulse abnormalities, such as inequality and asynchronism and the less common unilateral absence of pulsation, are not infrequently discussed in the literature. Inequality in the size of the pulse wave in two similar arteries is probably the most frequent abnormal observation. Asynchronism of the pulse wave is also not infrequent. Unilateral absence of pulsation has been reported as occurring most often in the radial arteries, but it has been known to occur in the carotid, brachial and radial arteries of one side.

Hare and Holder² analyzed the observations in 953 cases of thoracic aneurysm and called attention to the abnormalities of the pulse. Of this number, 570 were cases in which the aneurysm was of the ascending portion of the arch, and pulse abnormality occurred in 13 of these.

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* From the Department of Internal Medicine, University of Michigan, Ann Arbor, Mich.

1. Boyd, L. J.: A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta, *Am. J. M. Sc.* **168**:654 (Nov.) 1924.

2. Hare, H. A., and Holder, C. H.: Some Facts in Regard to Aneurysm of the Aorta, *Am. J. M. Sc.* **118**:399 (Oct.) 1899.

In 8, the right radial pulse was greater than the left; in 4, the left was greater than the right, and in 1, the pulse was absent in the left axillary, brachial, radial and carotid arteries. Aneurysm of the transverse arch occurred 104 times in the total group. Here pulse abnormality was noted 15 times, the left radial pulse being absent in 2, and the left being weaker than the right radial pulse in the remaining 13. In 110 cases of aneurysm of the descending portion of the aortic arch, the pulse was observed to be absent in the left radial artery in 2, and weaker than the right in 2 other instances. In the total number of reports of these cases there was no mention of bilateral absence of pulsation.

Pulse abnormalities have been recognized by careful observers of the last century as illustrated in the treatises by Corvisart,³ Bertin,⁴ Flint⁵ and Fuller.⁶ However, these astute clinicians have left no record of the absence of arterial pulsation occurring bilaterally. In the literature of the past two decades, such as the papers by Findlay,⁷ Arnold,⁸ Kahn⁹ and others, time and space have been given to pulse inequalities, but no mention has been made of the remarkable observation under discussion in this paper. This also applies to the complete modern textbooks, such as those by Strümpell,¹⁰ Külbs,¹¹ Hirschfelder,¹² Dieulafoy¹³ and the modern American Systems of Medicine.¹⁴

Thus we see that in the literature of the last century and a quarter, dealing with the signs in aneurysm, unilateral pulse abnormality is commonly recognized, but there has been a universal lack of discussion of absence of arterial pulsation on both sides. There is only one

3. Corvisart, J. N.: *Essay on Organic Diseases and Lesions of the Heart and Great Vessels* (Trans.), Philadelphia, 1812.

4. Bertin: *Treatise on Diseases of the Heart and Great Vessels*, Philadelphia, 1833.

5. Flint, Austin: *A Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart*, Philadelphia, 1859.

6. Fuller, H. W.: *Diseases of the Heart and Great Vessels*, London, 1863.

7. Findlay, L.: *On Delay or Retardation of the Pulse as a Sign of Aneurysm*, *Practitioner* **83**:803 (Dec.) 1909.

8. Arnold, H. D.: *Importance of the Early Detection of Aneurysm of the Aorta*, *Am. J. M. Sc.* **135**:515 (April) 1908.

9. Kahn, M. H.: *Pulse Difference in Aneurysm of the Arch of the Aorta*, *M. Clin. North America* **8**:347 (July) 1924.

10. Strümpell, A.: *Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten*, Leipzig, 1928, vol. 1, 578.

11. Külbs, F.: *Handbuch der inneren Medizin*, Berlin, 1928, vol. 2, p. 1, 476.

12. Hirschfelder, A. D.: *Diseases of the Heart and Aorta*, Philadelphia, 1913.

13. Dieulafoy, G.: *Textbook of Medicine*, New York, 1914, vol. 1, p. 512.

14. Tice: *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, 1924; *Oxford Medicine*, New York, Oxford University Press, 1928; *Nelson's Loose-Leaf Living Medicine*, New York, T. Nelson & Sons, 1920.

exception to this. Osler¹⁵ mentioned that it has been reported that there has been complete absence of the pulse in the arteries of the head and upper extremities in large aneurysm of the transverse arch. (Incidentally, he reported an instance of obliteration of the pulse in the abdominal aorta and in both lower extremities in the presence of aneurysm of the abdominal aorta.)

Three isolated reports are available in the literature, of cases in which there was obliteration of the pulse in the arteries of the upper extremities. In two of these there was also lack of pulsation in the arteries of the neck. These reports of cases are reviewed below and we have added our report of a case as a fourth.

CASE REPORTS

The first case is one reported by Broadbent,¹⁶ before the Clinical Society of London in 1875.

A laborer, aged 50, was admitted to the hospital because of ascites and chronic bronchitis with emphysema. He had been a sailor and had had syphilis. The ascites was presumed to have as a basis hepatic cirrhosis, and during the seven months before his death paracentesis was done frequently.

Of particular interest was the circulation of the upper extremities, and we shall quote this description. "There was no pulse at either wrist, but while this was the case, the radial arteries could be distinctly felt full of blood and could be rolled under the finger. That this cord-like object under the fingers was really the radial artery was shown by the fact that when the arm was raised the blood receded, and the artery collapsed and became imperceptible. It should be added also, that from time to time, a faint flickering pulsation could be detected, more frequently and more perceptibly in the left than the right radial. The flow of the blood through the veins of the back of the hand and forearm was vigorous, and the hands were warm and presented no appearance of languid or deficient circulation. The muscular condition of the extremities was good. An additional interest was imparted to the condition by the statement of the patient that the absence of pulse had been detected (had come on as he said) after he had been thrown from a train in Boxmoor tunnel thirty years before. On further investigation, pulsation was found to be absent in the brachial and subclavian arteries; present in the left carotid, and feebly in the right; vigorous in the femorals and posterior tibials."

Examination demonstrated no abnormality of the heart, no abnormal pulsation and no dulness in the upper part of the chest. In other words, Broadbent said, there was no evidence for the diagnosis of aneurysm or intrathoracic tumor.

Broadbent was frankly puzzled by the observations and kept the patient under observation until his death. At necropsy, the heart was essentially normal. The aorta was slightly enlarged; otherwise it appeared unaltered. When it was opened, there was found little disease of the internal coat, and the wall was elastic. To quote: "It was seen, however, that the orifices of the innominate and the left

15. Osler, William: *Modern Medicine*, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 864.

16. Broadbent, W. H.: *Absence of Pulsation in Both Radial Arteries the Vessels Being Full of Blood*, Tr. Clinical Society, London, 1875.

carotid arteries were close together, and the mouth of the former was exceedingly small. The innominate was found not only to be narrowed at its origin, but rigid. An atheromatous patch surrounded the mouth of the vessel involving the structures both of the aorta and the innominate; it was hard and brittle and separated easily from the outer tunic. Immediately above its origin, the innominate enlarged to its usual size, and possessed its normal elasticity. Here, then, was the explanation of the absence of the pulse with a full vessel at the right wrist. It was found that the left vertebral artery, instead of arising from the subclavian, sprang from the aortic arch close to the origin of the subclavian, the orifice of which was narrowed to the size of a crow quill by the proximity of the vertebral. Here again atheroma had invaded the constricted orifice and rendered it rigid, while the artery beyond was healthy and of full diameter. The absence of pulsation in the two radials instead of being due to a single lesion, was thus caused by a repetition of a precisely similar condition at two separate points."

Comment.—Broadbent's report is the first in which bilateral absence of the pulse in the upper extremities is described. He was at a loss satisfactorily to explain his observations as indicated in the following sentence: "I was unable to frame, or to obtain from physicians who saw the patient, any explanation of the phenomenon described, or to find recorded cases throwing light upon them." In this case, we are not dealing with aneurysm as the basis for the obliteration of pulsation. According to the history, the patient had had syphilis, and a unilateral absence of pulse was alleged to have been present thirty years before. The pathologic observations explained the phenomenon, the atheroma accentuating and complicating a congenital anomaly in the origin of the vessels arising from the aortic arch.

The second case is that reported by Crawford¹⁷ in 1921, in which he found absence of arterial pulsation in both upper extremities and the neck, in the presence of thoracic aneurysm.

History.—A white man, aged 52, complained of severe occipital headache, pain in the back of the neck and shortness of breath. These symptoms had been of eighteen months' duration. The headache had been a constant feature, and dizziness and a tingling sensation in the left thumb had been present for twelve months. Six weeks before admission, during a "weak spell," the patient's wife had been unable to obtain the pulse. The patient said that he had had gonorrhea but not syphilis.

Examination.—The skin of the face and neck was dusky, and there was slight cyanosis of the lips and ears. The pupils were unequal, but pupillary reflexes were prompt. The superficial veins of the face, neck and chest were visible; those of the forearm were prominent. The radial and brachial arteries were palpable and compressible, but no pulsation was present in the vessels now in the carotids. The apex rate was 120 per minute. A diffuse slightly expansive pulsation was present in the upper two or three intercostal interspaces, more pronounced to the right of the sternum. Tracheal tug was present. The heart sounds were normal at the apex. A soft systolic murmur with a muffled second sound was heard at the second and third interspaces on either side of the sternum.

17. Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, J. A. M. A. 76:1395 (May 21) 1921.

No abnormality of pulsation was noted in the abdomen or lower extremities. The blood pressure in the lower extremities was 125 systolic.

A diagnosis of aneurysm was made and this was verified by fluoroscopic examination. The greater part of the arch and descending thoracic aorta was found to be involved. The blood gave a positive Wassermann reaction.

Comment.—In this patient there was found to be complete obliteration of the pulse in the radial, brachial and carotid arteries of both sides. This was apparently the condition six weeks earlier when the patient's wife, a trained nurse, failed to obtain the pulse. A diagnosis of aneurysm was verified roentgenologically, and the patient had a positive serologic reaction for syphilis. We wish to call attention particularly to the symptoms presented. Some of these were probably on a cardiac basis, but it should be emphasized that the patient had complained of constant headache for eighteen months, and dizziness for a year.

The third case is that reported by Shikhare¹⁸ in 1921.

A middle-aged man, a carpenter, entered the hospital because of attacks of dizziness. In the history, it was noted that the patient was subject to attacks of dizziness sometimes ending in syncope. During such attacks, he usually uttered a cry, and bending forward, would fall to the ground. Profuse perspiration accompanied the attacks.

Examination.—The patient was poorly nourished. He could hardly walk unsupported. There was marked intolerance to light, and ophthalmoscopic examination showed some patches of choroiditis. The outstanding observation was the absence of pulsation of all arteries of the upper half of the body. The arteries could be felt in their normal sites and, being somewhat rigid, could be rolled under the finger. The pulsation in the abdominal aorta and in the arteries of the lower extremities was normal. Cardiac examination was negative.

Necropsy.—The ascending aorta and the arch showed a fusiform aneurysmal dilatation which was occupied by a large antemortem clot obliterating almost the whole of its lumen. This large central clot sent projections into and almost obliterated the lumen of the innominate artery and its branches, the right common carotid and right subclavian, and also into the corresponding arteries of the left side to a variable extent. These finger-like projections acted as loosely fitting plugs for the different arteries mentioned, allowing a certain amount of blood to pass. There was a passage between the posterior surface of the central clot and the posterior aortic wall which probably allowed a fair amount of blood to pass to the descending aorta.

Comment.—In this patient also, in whom there was a bilateral lack of pulse wave in the arteries of the upper extremities and neck, the aortic lesion present was that of aneurysm. The anatomic observation of a large clot in the aneurysmal sac is of great interest. Though the trunk vessels arising from the aortic arch were almost completely obstructed by projections of the clot into them, enough blood apparently

18. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, *Indian J. Med.* 2:326 (March) 1921.

passed so that nutrition of tissues was maintained. However, the obstruction prevented transmission of the pulse wave to the column of blood in the affected vessels.

Although the history is meager, we again wish to call attention to the major symptom. Frequent attacks of dizziness going on to syncope brought the patient for medical attention.

The fourth case is that which prompted the collection of this series of reports. This patient was observed by us for a short time in the wards of the University Hospital.

F. K., an Austrian factory laborer, aged 35, entered the University Hospital in October, 1928, complaining of dizziness and fainting attacks.

History.—Seven weeks before admission to the hospital, the patient suddenly became dizzy and nauseated while at work. Everything became black before his eyes, and he fell to the floor unconscious. He was unconscious only a few seconds and recovered when his fellow workmen lifted him to his feet. For three weeks, the patient was troubled daily with dizzy attacks in which he would have to support himself to keep from falling. At times he did fall unconscious. At the end of this period, he went to bed and remained there until his admission to the hospital. During the period spent in bed, he was dizzy only when getting up, and on one such occasion fell unconscious. At times, vision was poor in that everything appeared dark, but at such times he was neither dizzy nor nauseated.

For six years, the patient had had pain over the front of the chest, the pain being dull and lasting only a few moments. During the past seven weeks, the pains had been more frequent and more severe, occurring either over the right or the left side of the chest in front.

Appendectomy was done four years before, and two years later laparotomy was necessary for acute intestinal obstruction. The patient stated that on that admission to the hospital the left pulse at the wrist could not be obtained. Of importance is the history of a primary genital lesion in 1917. There had been a loss of 30 pounds (13.6 Kg.) in the past two years.

The patient was married, but the wife had never been pregnant.

Physical Examination.—The patient was a well developed man, apparently comfortable in bed either lying down or sitting up. The head was normal. The pupils were round and equal and reacted promptly to light and in accommodation. The nose, mouth and throat were normal. There was no huskiness of the voice. The larynx appeared normal. A slight but definite tracheal tug was present.

The chest appeared to be symmetrical, but there was lagging and decreased expansion of the left side on inspiration. Respirations were normal. There was a diffuse heaving impulse over the whole upper part of the chest, more marked over the left upper part of the chest and precordium. This was synchronous with the heart beat. Retromanubrial dullness was increased to both sides in the first and second interspaces, especially to the left. The cardiac apex impulse was visible in the fifth interspace 10 cm. from the midsternal line. On auscultation there was noted some tachycardia, but rhythm was regular. The heart sounds were of fair quality. The second sound at the base was ringing in character. To the right of the sternum in the second intercostal space and extending to the right infraclavicular region were heard a high pitched blowing systolic murmur and a lower pitched short diastolic murmur.

The radial and brachial arteries could be palpated, and were full, but no pulse was present. The absence of pulsation was noted also over the carotid arteries

and their superficial branches. The pulsation of the abdominal aorta was normal, and arteries of the lower extremities showed a normal pulse down to and including the dorsalis pedis. The upper extremities showed no evidence of impaired circulation, being of normal color, warm and with normal mobility. There was rapid return of color following pressure on skin or nail beds. No clubbing of the fingers was present nor incurvature of the nails. The blood pressure as obtained in the lower extremities was 178 systolic with 110 diastolic.

There was no evidence of venous stasis in the arms or upper part of the chest as might be expected in mediastinal pressure. No abnormal pulsations could be made out over the anterior surface of the chest which would indicate a collateral circulation. Posteriorly, at the angle of the left scapula in the eighth interspace was a visible and palpable pulsation, demonstrable only over a length of about 2 cm. This was synchronous with systole. There was no comparable pulsation on the opposite side.

The remainder of the physical examination was negative, except for a generalized lymphadenopathy including the cervical, axillary, epitrochlear and inguinal glands. The spine was normal, except for a slight dorsal kyphoscoliosis. Reflexes were normal.

Technical Examinations.—Examinations of the urine and stools yielded negative results on all occasions. The blood showed a hemoglobin content of 85 per cent, a red cell count of 4,600,000 and a white cell count of 9,700 with a normal blood smear. The Kahn test was 4 plus. The roentgenologist reported a wide mediastinal pulsating shadow bulging to the left, and made a diagnosis of aneurysm of the ascending and transverse portions of the aortic arch. An electrocardiogram showed only sinus tachycardia.

Comment.—In this patient, in whose case a diagnosis of aortic aneurysm was substantiated by roentgenologic examination, there was obliteration of the pulse in the arteries of the upper extremities and of both sides of the neck. Of interest is the fact that an area of pulsation was present in the region of the angle of the left scapula. Again we wish to emphasize that the symptom which brought the patient to the hospital was dizziness occurring in attacks leading, at times, to unconsciousness.

EXPLANATION OF ABSENCE OF PULSATION

Several explanations have been advanced for the phenomena of pulse inequality or absence of pulse in the arteries of the upper portion of the body. Though the available discussions on this phase of the subject have, almost without exception, dealt merely with pulse inequality or at most with unilateral absence of pulse, the explanations offered may be carried over into a discussion of the bilateral obliteration of arterial pulsation.

The most universal explanation offered for unilateral absence of pulsation has been on the basis of hydrodynamics, in that a large distensible sac may so absorb the force of the cardiac systole that an intermittent stream is converted into a continuous one. Osler¹⁵ quoted Harvey to this effect, and experimental work by Marey¹³ bore

out this supposition. Kahn⁹ advanced this explanation as one of several for pulse obliteration.

A second explanation offered for abnormality in the pulse is that of thrombus formation within the aneurysmal sac. Kahn⁹ and Dieulafoy¹³ agreed that such a thrombus may partially obstruct the orifice of an arterial trunk arising from the sac. Such encroachment on the opening of an artery would diminish the flow of blood into it and as a result the pulsation usually transmitted would be lost. In Shikhare's case, an advanced degree of such a condition was demonstrated in that projections from the large main thrombus fitted as loose plugs into the arteries arising from the sac.

Another explanation offered by authors, such as Flint,⁵ Kahn,⁹ Strümpell¹⁰ and Sansom,¹⁹ is that an artery leading from the aorta may be obliterated to some degree by pressure on it by the aneurysmal sac. Flint⁵ stated specifically that the aneurysmal tumor may press on the subclavian, carotid or innominate artery. In such case, the pulse abnormality is merely one of several possible pressure phenomena. Though no certain conclusions can be drawn from Crawford's case, the physical observations as described for his patient suggest pressure as a possible cause for pulse obliteration. It may be pointed out that he described dusiness and cyanosis of the face and lips, and inequality of the pupils, and said that the superficial veins of the face and upper part of the chest were visible, those of the forearm being prominent. These details are suggestive of pressure in the mediastinum.

Narrowing or distortion of the orifice of one or more of the arteries arising from the aorta may explain pulse abnormalities. Strümpell¹⁰ said that this may occur in arterial trunks arising from an aneurysmal sac. Osler¹⁵ maintained that pulse inequality is most frequently on this basis in the presence of aneurysm. That atheroma at an arterial orifice may play a part is accepted by Dieulafoy.¹³ Although Broadbent's case is not one of aneurysm, the pulse obliteration was due to such circumstances. He said that as a result of the atheroma the arteries were cut off from the general expansive movement of the aorta, and that a small stream, insufficient to distend the peripheral arteries, was allowed to pass.

Since congenital variation in the origin of the arterial trunks from the aortic arch is not rare, it is conceivable that such an anomaly might occur coincident with such a common lesion as aneurysm. In such an event, owing to fewer trunk arteries, the possibility of bilateral absence of pulse would be enhanced. In the case of Broadbent's patient, there was an anomalous pattern in the arteries springing from the aortic arch.

19. Sansom, A. E.: *Twentieth Century Practice of Medicine*, New York, 1895, vol. 4, p. 505.

Because narrowing of an orifice by local changes, or obstruction by a thrombus can occur, it is possible that such a process might slowly progress until complete obliteration of the trunk artery is produced. In such an event, a collateral circulation would need to take up the burden of supplying blood to the parts cut off from their normal supply. In case of bilateral obliteration of the pulse, the complete obstruction with collateral circulation would not need to be bilateral. In fact, it might more probably be unilateral owing to either a more extensive or a more prolonged involvement on one side. In our patient, such a possibility may be considered. The pulsation at the angle of the left scapula undoubtedly was produced by the intercostal artery and so suggests a collateral circulation in which the intercostal arteries were involved. Obliteration at the orifice of the left subclavian due to whatever cause might well lead to a collateral circulation involving the intercostal and the internal mammary arteries. From this point of view, it is of interest that two years before, the left radial pulse was absent. Thus the etiologic factor, whether thrombus or local change at the orifice, may have involved the left subclavian first or more extensively than the innominate, or left carotid, and later may have led to complete obliteration with a resultant collateral circulation on that side. Complete obstruction at the origin of the subclavian by pressure from the aneurysmal sac is not probable in the absence of other pressure phenomena.

COMMENT

Because of the rarity of the remarkable condition under discussion in this paper, it was thought to be of sufficient interest to collect the three available reports from the literature and review these with our case. Inequality of pulses or unilateral absence of pulsation is not infrequent.

Syphilis presumably was the etiologic factor in the aortic lesion in each of the collected cases. In Broadbent's case there was a history of syphilis, and pathologically lesions were present in the aorta at the orifices of the arterial trunks. Such changes in a man of 50 years, with a history indicating pulse abnormality for many years make syphilis most probable. In Crawford's case, and in our case, the diagnosis of aneurysm was verified roentgenologically, and in each there was serologic evidence of syphilis. Shikhare gave no serologic data, but the observation at necropsy of aortic aneurysm in a middle-aged man is presumptive evidence of syphilis.

We believe it to be important to direct attention to the symptoms which caused the patients to seek medical attention. In the three patients suffering from aneurysm, the complaints were almost identical and indicate deficient blood supply to the brain. Occipital headaches, dizziness, syncope, nausea and visual impairment constituted this group

of symptoms. Broadbent dwelt on other features of the history in his patient and failed to mention similar symptoms.

From a physical standpoint, there was absence of arterial pulsation in the neck and upper extremities in all the collected cases, with the exception of a weak carotid pulse on one side in Broadbent's patient. In one subject, some signs in the examination indicated possible pressure phenomena. Otherwise, the parts supplied by the pulseless arteries failed to demonstrate any physical evidence of deficient circulation. In all, the parts were warm, of normal nutrition and of good color. In our patient there was a rapid return of color after the release of pressure on the skin or nail bed.

The varied explanations of pulse inequality and unilateral absence of pulsation which have been advanced from time to time have been considered and applied to the lack of the pulse bilaterally. We have discussed the possibility of complete obliteration of an arterial trunk with a resultant collateral circulation. The history and examination in our patient presented data warranting the consideration of this possibility.

SUMMARY AND CONCLUSIONS

1. Three available case reports of the bilateral absence of pulse in the radial, brachial and carotid arteries have been collected from the literature. We have added a fourth.

2. Though pulse inequality and unilateral absence of pulse are not infrequently mentioned in the literature, the obliteration of the pulse bilaterally undoubtedly is rare, since practically no reference is made to it in the many discussions on signs in aneurysm.

3. Syphilis was unquestionably present in the four collected cases; in three there was aneurysm of the aorta.

4. The accepted explanations for pulse inequality in the presence of aneurysm may be applied in the condition under discussion.

5. It is possible that a process causing partial obstruction to an arterial orifice may lead to complete occlusion with a resultant collateral circulation.

6. From the histories as given in the case reports, it may be concluded that in like instances symptoms resulting from deficient cerebral blood supply will probably cause the patient to seek medical advice. Attacks of dizziness leading to syncope were the most striking symptom in each of the patients suffering from aneurysm with absence of arterial pulse in the neck and upper extremities.

Pueblo Clinic, Pueblo, Colo.

Henry Ford Hospital, Detroit.

ABDOMINAL EXPLORATION IN CASES DIAGNOSED CHOLECYSTITIS OR CHOLELITHIASIS BEFORE OPERATION *

ANDREW B. RIVERS, M.D.

AND

HOWARD R. HARTMAN, M.D.

ROCHESTER, MINN.

In a previous paper we¹ reported the results of abdominal exploration undertaken during operation for gastric or duodenal ulcer. A large variety of pathologic conditions, which had escaped detection preoperatively, were detected during laparotomy. Some of these conditions were merely of academic interest and probably were not productive of significant symptoms. Others were sufficiently masked by symptoms related to the disease of major importance to escape detection. Some were of definite clinical importance and should have been recognized preoperatively.

In reviewing the records of a large number of patients who had undergone cholecystectomy for cholecystitis or cholelithiasis, we became impressed by the large variety of associated diseases which were found. We believed that it might be of some interest (1) to tabulate the diseases most frequently found associated with cholecystitis or cholelithiasis; (2) to ascertain which diseases most frequently mask themselves in the syndrome of disease of the gallbladder and thus escape preoperative comment, endeavoring to determine whether, by any signs, the presence of these diseases should have been suspected by the examining clinician or surgeon, and (3) to focus our attention especially on the more important rare complications, thus gathering information which might help us in detecting them.

The records of 879 patients were studied. In selecting these records, we had the advantage not only of the surgeon's judgment in regard to his observations but of the opinions expressed by the pathologists who studied the removed specimens.

In all of the cases, pathologic conditions in the gallbladder were sufficient to warrant its removal. In many instances, unusual complications were discovered only after the minutest study of the removed tissues.

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* From the Division of Medicine, the Mayo Clinic.

1. Hartman, H. R., and Rivers, A. B.: Benign Gastric and Duodenal Ulcer: The Clinical Diagnosis and the Conditions Found at Operation, *Arch. Int. Med.* **44**:314 (Sept.) 1929.

A prerequisite to the acceptance of these records for study was that they include only a single relevant preoperative diagnosis, such as cholelithiasis. Thus, for instance, cases in which the diagnosis was cholecystitis or duodenal ulcer were not included. Cases in which there was a dual diagnosis of independent conditions, such as cholecystitis and mature cataract of the left eye, were not rejected for study because obviously such irrelevant conditions could scarcely affect the preopera-

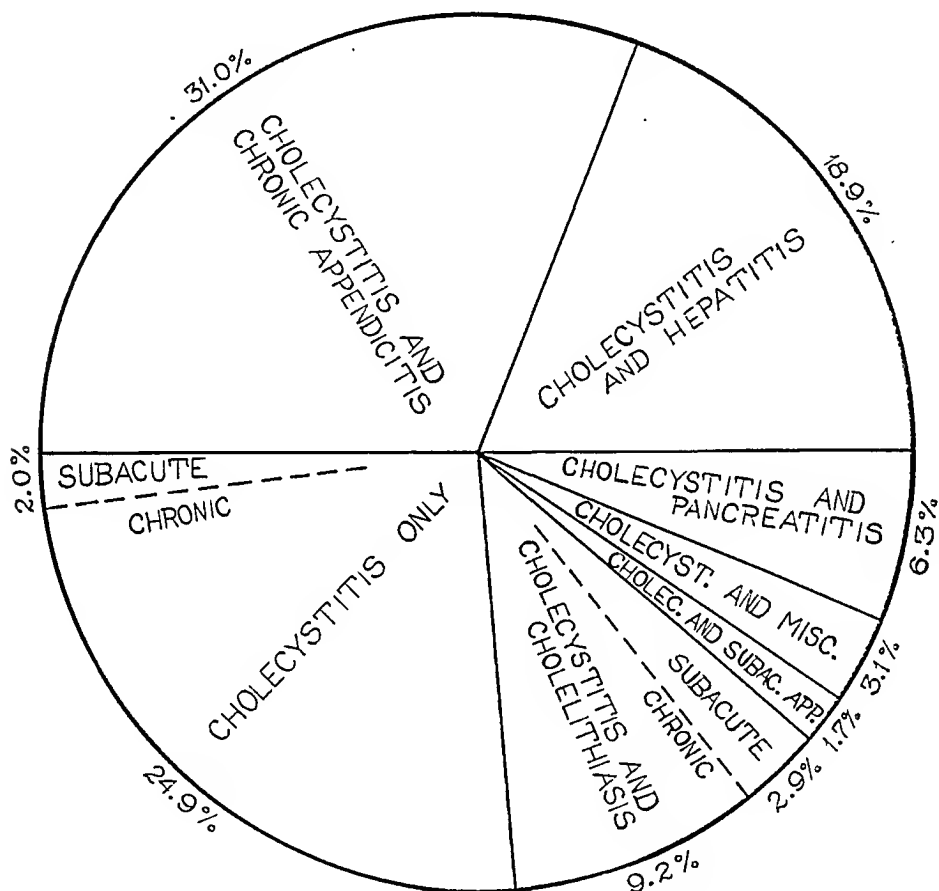


Chart 1.—Conditions found at operation in 287 cases in which the preoperative diagnosis was of cholecystitis only: *Misc.* indicates miscellaneous conditions as follows: duodenal ulcer, four cases; duodenitis, one case; cholangitis, one case; accessory lobes of the liver, one case; myoma of the anterior wall of the stomach, one case; Lane's kink, one case, and cholecystoduodenal fistula, one case; *subac. ap.* indicates subacute appendicitis.

tive clinical history. In 287 of these cases, the preoperative diagnosis was cholecystitis, and in 592 operation was undertaken on the diagnosis of cholelithiasis.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS CHOLECYSTITIS ONLY

Cases in which the preoperative diagnosis was cholecystitis were studied separately. The complications have been listed diagrammatically

so that the frequency, in percentage, of each complication becomes readily apparent. In chart 1, we have represented diagrammatically the diverse pathologic entities encountered during operations which were performed after a preoperative diagnosis of cholecystitis had been made; these preoperative diagnoses did not include any mention of cholelithiasis. In these cases, the diagnosis of chronic cholecystitis was corroborated at operation, but in 71 per cent of the cases some additional condition, either of the gallbladder or of other organs, and not specifically mentioned preoperatively, was discovered. In 2 per cent of the cases, subacute cholecystitis was found uncomplicated by any other pathologic condition. Thirty-one per cent of these cases were complicated by chronic appendicitis; 1.7 per cent by subacute appendicitis; 18.9 per cent by associated hepatitis, and 6.3 per cent by pancreatitis. In 12.1 per cent of these cases, gallstones were found, although their presence had not been suspected before operation. Among those cases grouped under the heading miscellaneous were four of duodenal ulcer, one of duodenitis, one of cholangitis, one of myoma in the anterior wall of the stomach, one of Lane's kink, one of cholecystoduodenal fistula and one of accessory lobes of the liver.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS CHOLELITHIASIS ONLY

Chart 2 represents diagrammatically those cases in which operation was done after a diagnosis of gallstones had been made preoperatively. In all these cases, sufficient pathologic change was demonstrable in the gallbladder to warrant its removal, but gallstones were present in only 84.8 per cent. In 28.9 per cent of the cases associated chronic appendicitis was found, in 2.5 per cent subacute appendicitis, in 12.7 per cent hepatitis, in 7.8 per cent pancreatitis, and in 1.1 per cent cholangitis. It is suggested, therefore, that the diagnosis of cholelithiasis is not so easily made as one is frequently led to believe. In this group cholecystitis only was found in 15.2 per cent, and yet the symptoms were obviously sufficiently severe to prompt the preoperative diagnosis of cholelithiasis.

CASES IN WHICH THE PREOPERATIVE DIAGNOSIS WAS EITHER CHOLECYSTITIS OR CHOLELITHIASIS

Chart 3 includes cases in which a preoperative diagnosis either of cholecystitis or of cholelithiasis had been made, and represents a review of 879 cases. In order to facilitate consideration of these cases, they have been subdivided into groups as follows:

Group 1.—In this group, chronic cholecystitis, with or without stones, was discovered at operation and other abnormalities were not discovered. In 35.6 per cent of the cases, a chronically inflamed gall-

bladder was found. In 6.6 per cent, there was evidence at operation of subacute inflammation but in none of these was there any notation on the chart that a subacute condition had been suspected before operation. Although, occasionally, a subacutely infected gallbladder is not productive of signs characteristic of this condition, the history usually includes some data which would aid in its preoperative recognition. There may be chills or fever or leukocytosis. Usually there

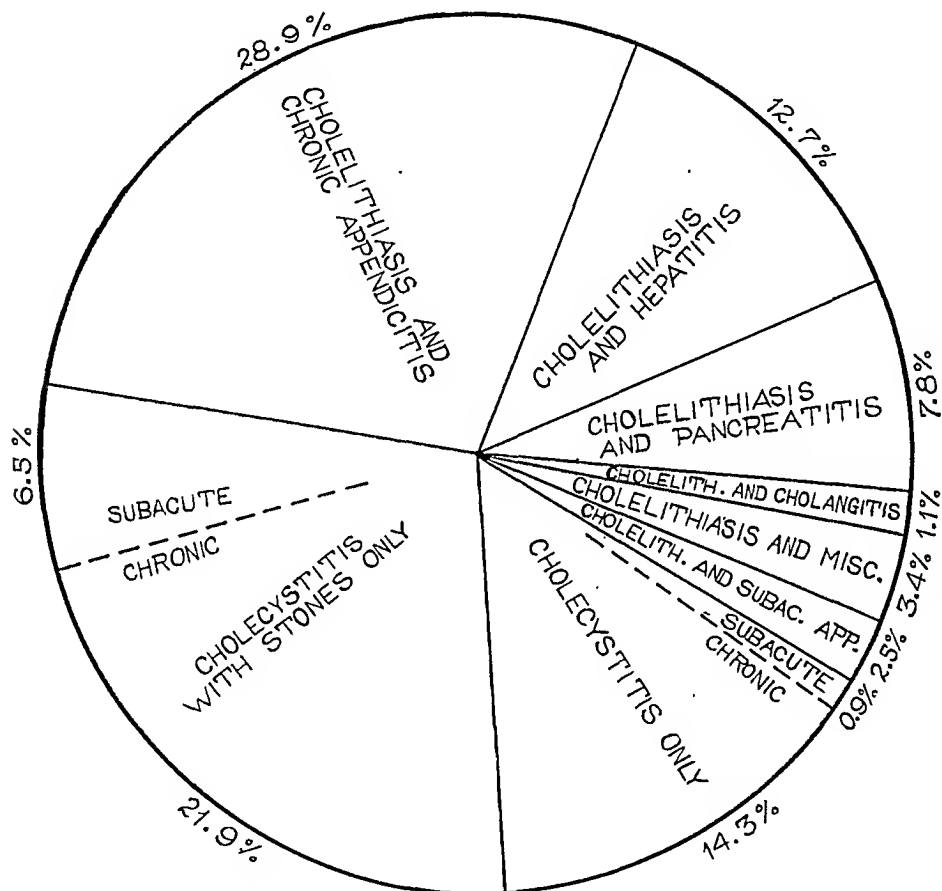


Chart 2.—Conditions found at operation in 592 cases in which the preoperative diagnosis was cholelithiasis only: *Misc.* indicates miscellaneous conditions as follows: duodenal ulcer, four cases; gastric ulcer, one case; ulcer near the fundus of the gallbladder, one case; carcinomatous growth of the common and cystic ducts, one case; carcinoma in the fundus of the gallbladder, one case; questionable carcinoma of the pancreas and common bile duct, one case; questionable carcinoma of the pancreas, one case; carcinoma of the liver, one case; cyst of the liver, one case; cyst of the wall of the gallbladder, one case; accessory liver, one case; angioma on the surface of the liver, one case; adenomyoma and epithelioma of the gallbladder, one case; adenoma at the fundus of the gallbladder, one case; adenoma of the abdominal wall with hyperplasia of the epidermis, one case; inflammatory lymph node filled with pigment, one case; fibroma of the gastro-hepatic omentum, one case; diverticulum of the gallbladder, two cases; questionable duodenal diverticulum, one case; Lane's kink, one case, and cholecystoduodenal fistula, two cases.

is definite, localized tenderness and, not infrequently, rigidity of the overlying abdominal wall. In 58 per cent of the total number of cases included in this group, some disease besides that mentioned in the preoperative diagnosis was found at exploration.

Group 2.—Cholecystitis and hepatitis, cholecystitis and pancreatitis, or cholecystitis and cholangitis were found at operation in cases classified in this group. Much has been written regarding the relationship

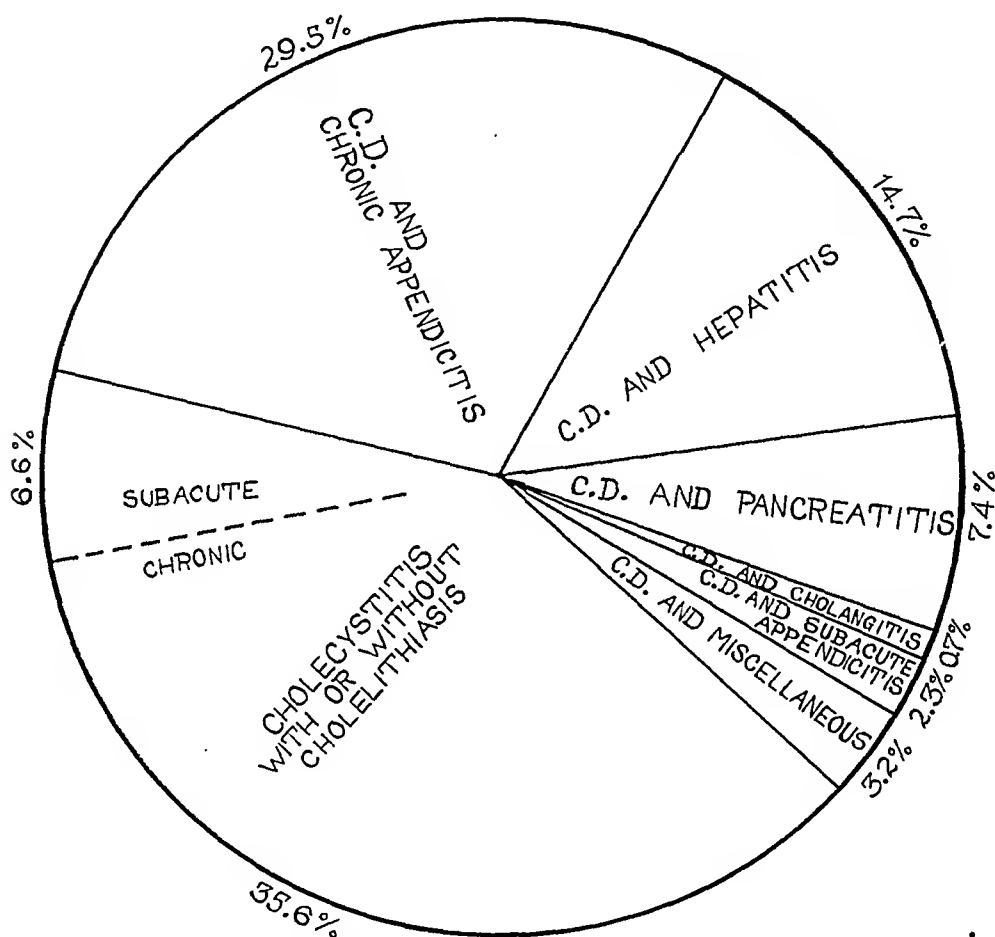


Chart 3.—Conditions found at operation in the total series of 879 cases in which the preoperative diagnosis was either cholecystitis or cholelithiasis: *C.D.* indicates cholecystic disease, which here includes cholecystitis, cholelithiasis, or both.

of disease of the gallbladder to hepatitis, pancreatitis and cholangitis. In this series of cases, the surgeon's diagnosis of these complications was accepted. In 14.7 per cent of cases, hepatitis was found associated with the pathologic condition of the gallbladder. In 7.4 per cent of the cases, pancreatitis was a complication, and cholangitis was found in 0.7 per cent. Inflammatory changes in the liver occur frequently when there is infection in the gallbladder.

Mentzer² carried on an extensive study in this field. His material was obtained from 548 cases in which cholecystitis or cholelithiasis was found at necropsy. He studied sections from different regions of the liver and concluded that "the cases of noninflammatory disease of the gallbladder (minor gross lesions such as adenomas, diverticula, adhesions to adjacent organs without other evidence of disease of the gallbladder and cholesterosis) show a relatively small percentage of associated hepatic disease, 60 per cent, as compared with the definitely inflammatory diseases, such as gallstones, 97 per cent." Pancreatitis is a more rare complication of disease of the gallbladder. Mayo³ stated that pancreatitis is found associated in 7 per cent of cases in which gallstones are present. In the series under consideration, there was evidence, on microscopic examination, of some degree of pancreatitis in 7.4 per cent of the cases of cholecystitis and cholelithiasis, taken together.

Cholangitis seems to be a rare complication of disease of the gallbladder; it occurred in only 6 of the 879 cases included in this group.

Group 3.—Chronic, acute or subacute appendicitis was found at operation in this group. The lesion most commonly found associated with cholecystitis or cholelithiasis was chronic appendicitis; in 31.8 per cent of the cases, there was associated disease in the appendix. Undoubtedly this percentage would be still greater but for the fact that in a number of cases appendectomy had been performed before the patients came to the clinic. The frequency of this complication must not lead one to attach too much significance to it. Although a chronically inflamed appendix may, in a limited number of patients of a particularly sensitive make-up, be productive of some dyspepsia, it is debatable whether in the majority of the cases under present consideration, the history was greatly influenced by the presence of this complication. What seems of greater significance is the fact that in approximately 2 per cent of these patients acute or subacute appendicitis remained sufficiently masked in the syndrome of disease of the gallbladder to avoid detection by the examining physician. The relatively greater severity of symptoms of disease in the upper part of the abdomen may have led these patients to ignore the distress in the lower abdominal segment. Thus they might have failed to mention having pain in the region of the appendix.

It must also be remembered that occasionally an acutely inflamed appendix will cause such mild symptoms that they may be considered

2. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, *Surg. Gynec. Obst.* **42**:782, 1926.

3. Mayo, W. J.: Pancreatitis Resulting from Gallstone Disease, *J. A. M. A.* **50**:1161 (April 11) 1908.

of trivial significance. Nevertheless, one wonders whether more careful general examinations might have revealed definite tenderness in the lower part of the abdomen and thus might have led to correct diagnosis more frequently.

Group 4.—In this group has been placed a large variety of the less common complications found in association with cholecystitis or cholelithiasis. A further subdivision of this group has been made to facilitate discussion. Several reports of cases will be included.

Duodenitis: The patient had had dyspepsia at intervals for several years, with much gas and pain in the upper right quadrant of the abdomen. Distress was worse two hours after meals. Greasy and fried foods usually had been followed by dyspepsia. At operation, cholecystitis and definite duodenitis were found. It is difficult to state which lesion could be held accountable for the symptoms. Although the gallbladder showed enough evidence of involvement to warrant its removal, it would seem probable that the symptoms were related to the duodenitis. It has been pointed out by one of us (Rivers)⁴ that duodenitis frequently is responsible for a syndrome such as that described in this case.

Gastric Ulcer: This patient had had intervals of colicky epigastric pain for twenty-nine years. The distress was described as a colicky pain referred through to the back, relieved by vomiting and usually lasting a few hours. The acidity of the gastric content was low. In all probability, the symptoms were due to the gallstones.

In 2 per cent of patients operated on for gastric ulcer, associated disease in the gallbladder was found. Reliable evidence of the presence of an active ulcer is the clinical history. Healed or quiescent ulcers are not uncommon.

Duodenal Ulcer: There were eight cases in which disease of the gallbladder was associated with duodenal ulcer. In none of these eight was there evidence roentgenologically of duodenal deformity, but in four cases the Graham-Cole method of roentgenography gave evidence that the gallbladder was diseased. It would appear that the clinician was unduly influenced in making his diagnosis by the roentgenologic results found in these cases. Abstracts of two illustrative cases follow:

In one case, the presence of both the ulcer and the gallstones should have been suspected. There was a history of colicky epigastric pain, coming in spells, and requiring hypodermic injections of hypnotics for relief. In addition, the history suggested peptic ulcer; that is, there had been epigastric distress from two to three hours after meals which had been relieved by the taking of food. The other patient

4. Rivers, A. B.: A Clinical Study of Duodenitis, Gastritis and Gastrojejunitis, Pennsylvania M. J., to be published.

complained of colicky epigastric pains radiating through to the back. They had come on in spells, and at times hypodermic injection of morphine had been required for their control. The symptoms in this case were obviously related to the gallstones. At operation, duodenal ulcer and cholelithiasis were discovered.

Cholecystoduodenal Fistula: In this series, there were four cases in which a fistula was found to exist between the gallbladder and the duodenum. We believe that these cases are of sufficient importance to warrant a brief review of the histories.

The first patient had had a vague type of dyspepsia usually associated with migraine at intervals for seventeen years. Three years before the patient came to the clinic, severe pain had appeared in the upper right quadrant of the abdomen, radiating through to the back and to the right shoulder. Intermittent attacks had come on in spite of careful diet. There had been one severe spell recently, with pain so severe that the entire right side of the abdomen had seemed paralyzed. The gallbladder was not visualized by the Graham-Cole method. At operation, the gallbladder was found to be almost completely destroyed. Gallstones were not present. There was a fistula between the gallbladder and the duodenum.

The second patient, a woman, aged 59, had had an attack of acute indigestion accompanied by chills, fever, vomiting and very severe pain in the upper right abdominal quadrant about twelve years before coming to the clinic. At that time her temperature had been elevated for from three to four days; she had been in a stupor for several days; jaundice had been intense, and she had been obliged to remain in bed for thirteen days. Since this attack, there had been much gas and belching after ordinary meals, especially if they contained fatty foods. She had not had any more acute attacks. By the Graham-Cole method, the gallbladder gave only a faint shadow. At operation, a perforation between the gallbladder and the duodenum and one gallstone were found.

The third patient, a woman, aged 40, had had a severe attack of epigastric pain before she came to the clinic; this had radiated to the upper right quadrant of the abdomen and through to the back. Morphine had been necessary for relief. For the following two years, she had had frequent attacks similar to the one just described. Three weeks before she entered the clinic she had had a very severe attack of pain in the right upper abdominal quadrant and back, had perspired freely and had had chills and vomiting; her temperature had been very high. Three days after the onset of the pain she had become jaundiced. At brief intervals following this, she had had severe stabbing pains in the upper right part of the abdomen. At operation, the gallbladder was found to be contracted. There were multiple gallstones, and a fistula was found between the gallbladder and the duodenum.

The fourth patient, a woman, aged 51, had had some dyspepsia for ten years. Fried, greasy food had caused belching and nausea. At intervals she had had some pain in the upper right abdominal quadrant, which had radiated to the right shoulder. One year before she came to the clinic, she had had a severe attack of pain which had required three hypodermic injections of morphine for its control. Since then, she had had an attack of acute indigestion about once every three months. On a few occasions, she had vomited blood during these attacks. The roentgenogram of the gallbladder, made according to the Graham-Cole

method, showed only a faint shadow. Stones could be visualized. At operation, the gallbladder was found to be full of pus and stones. It had ruptured, leaving a fistula extending to the duodenum.

Naunyn⁵ reviewed 384 cases of biliary fistula. Ninety-three of these were of the cholecystoduodenal type. The most common of the biliary fistulas are those between the gallbladder or biliary ducts and the intestine. Among these, the cholecystoduodenal fistula is the one most frequently seen. These fistulas may develop in several ways. The wall of the gallbladder may rupture, forming an abscess, and this in turn may rupture through into the duodenum. At other times, adhesions from repeated infections seal the gallbladder to the duodenum so that a perforation of the wall of either the gallbladder or a bile duct may lead directly to the formation of a fistula.

In one of the cases just reviewed gallstones were not found. It is possible, of course, that stones already had passed through the fistula into the intestine at the time the patient was operated on. The earlier history of jaundice further suggests such a succession of events. That fistulas may develop in acute conditions of the gallbladder, in the absence of gallstones, seems entirely possible, but actually this complication probably occurs infrequently, in the absence of stones in the gallbladder or bile ducts.

In the four cases just reviewed the clinical histories did not offer any definite diagnostic criteria which would lead one to suspect the presence of cholecystoduodenal fistula. The presence of complicated cholecystitis is suggested in all instances, however, by the unusually severe and protracted attacks of pain as well as by the severe chills and increased temperature, continued over a period of many days. The persistence of chills and fever, and the associated profound prostration, might suggest empyema of the gallbladder, but the severity of the pain seems to be out of all proportion to that usually experienced with this complication.

We are at present reviewing a large series of cases of cholecystoduodenal fistula and it is hoped that other data may be gathered which will give us further diagnostic criteria regarding this interesting complication.

Malignant Conditions: The cases in which malignant conditions were found during operations on the gallbladder seem of sufficient importance to demand individual consideration.

Carcinoma of common and cystic ducts. A man, aged 59, had begun to have attacks of severe pain in the upper part of the abdomen at the age of 51. The pain had been referred through to the back, and hypodermic injection of hypnotics had been necessary to control it. When the patient was about 55 years of

5. Naunyn, Bernhard: *A Treatise on Cholelithiasis*, London, The New Sydenham Society, 1896, p. 143.

age a sore spot had developed in the right infracostal region. This had remained sore at all times. He had lost 10 pounds (4.5 Kg.) in five years. Roentgenographic examination by the Graham-Cole method revealed a faint shadow. At operation a small stone was found in the common bile duct. The gallbladder was large and acutely inflamed. A mass, about 2.5 by 2 cm., was growing on the outer side of the cystic duct, at its juncture with the common bile duct. The gallbladder was removed. Choledochotomy was performed, and the growth was removed. It was found to be an adenocarcinoma.

Carcinoma of the liver. A patient, during operation for carcinoma of the rectum, had been found to have gallstones. Intra-abdominal metastasis was not found. At an operation seven months later, undertaken because the patient was having frequent severe attacks of pain in the upper right quadrant of the abdomen, two carcinomas of the liver besides the gallstones were found. In this case, the primary carcinoma in the rectum probably was the source of these lesions.

Carcinoma of the gallbladder. A woman, aged 50, had for twenty years had intervals of upper abdominal pain which had not radiated. The attacks had endured for from twenty minutes to one hour and at times morphine had been necessary to control the pain. At first these spells had occurred infrequently; during the past year, they had come on once or twice every fortnight. At operation, a distended gallbladder containing stones was found. The gallbladder was removed. During the laboratory examination, an adenocarcinoma was found in the fundus.

Adenomyoma and epithelioma of the gallbladder. A woman, aged 58, had had spells of colicky pain in the upper right quadrant of the abdomen for eleven years, the attacks becoming increasingly frequent. One week prior to consultation at the clinic she had had a severe attack of pain which had been accompanied by chills and fever. There had not been jaundice. At operation, the gallbladder was found to be chronically inflamed and to contain stones. In the laboratory, an adenomyoma was found in the submucosa and a microscopic epithelioma in the mucosa.

Carcinoma of the gallbladder and bile ducts is not a rare complication of disease of the gallbladder. Mayo⁶ found that carcinoma of the gallbladder was present in 2 per cent of a series of cases of cholelithiasis studied by him. For many years the relationship of gallstones and carcinoma of the gallbladder has been noted. Klebs and Willigk,⁷ in 1869, suggested that gallstones were the cause of carcinoma of the gallbladder. Courvoisier⁸ found gallstones in seventy-four of eighty-four cases of carcinoma of the gallbladder. We know of no reliable diagnostic criteria which can be employed in early cases of malignant disease of the gallbladder or bile ducts. In early cases, surgical operation offers a reasonable chance of cure. Later, when the diagnosis of this complication is suggested by loss of weight, cachexia and a mass in the region of the gallbladder, operation is usually of no avail.

6. Mayo, W. J.: *Carcinomata of the Gall-Bladder and Biliary Passages*, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic 2:144, 1910.

7. Klebs and Willigk, quoted by Naunyn (footnote 5).

8. Courvoisier, L. G.: *Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege*, Leipzig, F. C. W. Vogel, 1890.

Carcinoma of the pancreas. There were two cases in which carcinoma of the pancreas was found. The first patient, a woman, aged 65, had had a brief period of dyspepsia at the age of 64. Then, at intervals, she had had a transitory pain in the upper part of the abdomen which had been accompanied by some gas and bloating. Six weeks before coming to the clinic she had begun to notice some jaundice. This had become progressively deeper. At intervals she had had severe pain in the upper right quadrant of the abdomen, for the control of which morphine had been required. There was a small mass in the upper right abdominal quadrant. This was fairly well fixed, and was not tender. It moved somewhat with respiration. At operation, a large, distended gallbladder was found. There were large masses in the head of the pancreas which had every clinical appearance of being malignant.

The second patient, a man, aged 62, two years before coming to the clinic had begun to have attacks of indigestion, characterized by pain in the epigastrium, much belching, and chills and fever. These attacks had recurred at intervals of about two months. Several months prior to examination, he had begun to have chills and fever, which had persisted for about a month. Then he had become jaundiced and this condition had continued until the time of operation. Exploration revealed chronic cholecystitis and stones in the gallbladder and bile ducts. The head of the pancreas was enlarged and hard. It was assumed that this hardness was due to a malignant condition.

Carcinoma of the pancreas, unless it occurs in the head of the organ, is likely to be overlooked. When it is situated in the head of the pancreas, its presence frequently can be suspected because of the attendant, progressive jaundice without colic, the palpable gallbladder and cachexia. Eusterman studied a series of 138 cases of carcinoma of the pancreas. He found that in only about half the cases were there symptoms which suggested the presence of the lesion.

Other Complications: The following complications are not of great importance but are included because they complete the record of pathologic entities found during operation on the gallbladder after a simple preoperative diagnosis of cholecystitis or of cholelithiasis had been made. Diverticulum of the gallbladder was found twice. Accessory liver and Lane's kink were also found twice. The remaining conditions were found once: diverticulum of the duodenum, ulcer near the fundus of the gallbladder, myoma of the anterior wall of the stomach, angioma on the surface of the liver, adenoma at the fundus of the gallbladder, cyst of the wall of the gallbladder, cyst of the liver and inflammatory lymph node filled with pigment.

SUMMARY AND CONCLUSIONS

The diseases found in association with cholecystitis or cholelithiasis, when one of these has been considered the pathologic process of major importance, are represented graphically in charts 1, 2 and 3.

Analysis of the 879 reports included in this group revealed the presence of subacute cholecystitis or of subacute appendicitis in seventy-

eight instances. Additional care in obtaining histories, and especially careful general examination, should tend to lessen error in the recognition of these complications.

Gallstones were discovered at operation in 106 cases (12.1 per cent) when preoperatively a diagnosis of cholecystitis only had been made. Frequently, gallstones are not productive of severe pain.

Gallstones were not found at operation in about 15 per cent of the cases in which a preoperative diagnosis of cholelithiasis had been made. It would appear that the syndrome of cholecystitis frequently may include pain which is sufficiently severe to suggest the presence of gallstones.

The most significant of the complications discovered during operation performed for cholecystitis or cholelithiasis was found to be carcinoma involving the gallbladder, bile ducts or liver. Careful search through these histories did not reveal data which could have aided in the preoperative recognition of these complications.

Cholecystoduodenal fistula was found as one of the rare complications of disease of the gallbladder. This series included four such cases. Although it would have been impossible to diagnose this condition from the histories, the presence of some complications causing peritoneal irritation could have been suspected because of the unusually severe and protracted pain and because of the marked local and systemic reaction which was evident in each of these cases.

It would appear that modern diagnostic methods, correlating reliable laboratory data and carefully recorded histories, leave less than might be assumed for the surgeon to discover. The margin of safety in the liver permits much destruction of that organ before any symptoms are produced; mild hepatitis will go undiagnosed for a long time to come.

The surgeon's diagnosis of pancreatitis is always questionable as it is largely determined by the enlargement and induration present. The medical diagnosis of pancreatitis is still unreliable.

The presence or absence of gallstones, or the question whether the inflammatory reaction in the gallbladder is acute or subacute, is not of vital importance in a case of surgical cholecystitis.

Peptic ulceration of the stomach and duodenum, like gallstones, usually lends itself to easy diagnosis, and if active should be recognized from the history in spite of negative roentgenographic data.

Certainly better means of recognizing carcinoma are needed but odd, miscellaneous lesions probably will always be a surprise to the clinician after abdominal section.

THE TIME FACTOR IN THE ACTION OF PANCREATIC ENZYMES *

LAY MARTIN, M.D.

Instructor in Clinical Medicine at Johns Hopkins University

BALTIMORE

In an article published about a year and a half ago, Dr. Anthony Bassler¹ made the following statements:

1. All proteolytic enzymes are dual in their action of conversion. This is true of the one in the stomach as well as of that in the pancreatic juice, both of which require outside activation, that of the stomach from hydrochloric acid and that of the pancreas from a product of the duodenal mucosa (enterokinase).

By this I judge he meant that some other agent is necessary to activate these enzymes. Certainly he cites hydrochloric acid as being necessary to activate pepsin. As this may cause misunderstanding, let me say that what pepsin needs for activation is a medium in which the hydrogen ion concentration is within certain limits. The same factor is necessary for trypsin. Therefore, no more than diastase and lipase are they dual in their action of conversion.

He remarked that the action of the proteolytic enzymes is slow and went on to say:

2. As a general rule, this is not true of the diastatic ferments and in my work on diastatic activity with specimens from human beings and from animals, I found that in their action diastatic ferments closely correspond to a catalyzer; the action requires no time, incubation is almost unnecessary and it occurs at any reasonable temperature, even one that is considerably lower than that of the body. If one prepares tube 1 in the original test (namely, adding 1 cc. of duodenal return to 4 cc. of the starch solution) shakes it at once and tests for sugar with Benedict's or Fehling's solution, the sugar reaction will somewhat depend on the amount of diastatic ferment present; the test, however, is not accurate. Incubation for a considerable period of time does not cause much greater reaction. All that is necessary is to allow the mixture to stand for a minute or two at room temperature and definite conversion will occur.

Dr. Bassler was suggesting in this article the advantages of his starch method over a saccharogenic method² which I described in this journal about a year before. As his claim was mainly based on the reasoning quoted, it seemed that the following investigation might be of interest.

* Submitted for publication, Aug. 26, 1929.

* From the Gastro-Intestinal Clinic of the Johns Hopkins Hospital.

1. Bassler, A.: Arch. Int. Med. **41**:18 (Jan. 1) 1928.

2. Martin, L.: Arch. Int. Med. **39**:343 (March) 1927.

METHOD OF INVESTIGATION

Pancreatic Extract.—Five grams of powdered pancreatic extract was dissolved in 50 cc. of distilled water by shaking. This mixture was allowed to stand for at least four hours and was then filtered through Whatman no. 12 filter paper and a Mandler filter. The clear filtrate was then diluted with phosphate buffer³ of p_H 7.7 to 1:250 or 1:500 (adjusted so that the 30 minute tube would about equal the standard used).

One cubic centimeter of the diluted solution and 1 cc. of 1 per cent soluble starch solution (in phosphate buffer, p_H 7.7) were pipetted into Folin and Wu dextrose tubes, mixed and incubated for varying lengths of time. The tubes that were to be incubated longest were put in first so that all the tubes could come out at once, and the starch was not added to the Folin and Wu tube until just before it was to be incubated. The amount of sugar in each tube was then determined by the Benedict modification of the Folin and Wu method of determining blood dextrose.⁴ In table 1 are shown the results of three experiments.

Duodenal Return.—Pancreatic enzymes were obtained by drainage through a small caliber (no. 14 Levine) tube placed in the duodenum and kept there during

TABLE 1.—*The Effect of Incubation on the Power of Diastatic Enzymes in Pancreatic Extract to Convert Starch Into Sugar*

Minutes Incubated	Amount of Dextrose in Milligrams		
	Experiment 1	Experiment 2	Experiment 3
5.....	Too pale to read	Too pale to read	Too pale to read
10.....	Too pale to read	Too pale to read	Too pale to read
15.....	...	42	60
20.....	37	72	61
30.....	54	105	100
35.....	69
40.....	...	182	143
60.....	71	400	286

the entire process. The position of the tube was verified by fluoroscopy. When the tube was in place, about 40 cc. of 33 per cent magnesium sulphate was injected to start the flow of bile and pancreatic juice. The return was collected in 15 cc. centrifuge tubes until the drainage stopped. If more was desired, a second injection of magnesium sulphate was made. The tube containing the clearest and darkest fluid (B bile) was used for the determination of diastase. This tube was centrifugated at high speed for fifteen minutes. A small amount of the supernatant fluid was diluted to 1:600 with the phosphate buffer.³ The method of diluting a 1:600 solution was given in my original article.²

One cc. of the 1:600 dilution was pipetted into each Folin and Wu tube and treated with 1:0 cc. of 1 per cent starch solution in exactly the same manner as the pancreatic extract. The results may be seen in table 2.

The last case is that of hepatosis from arsphenamine intoxication. There was tremendous jaundice; no bile was excreted into the intestine. Consequently, the duodenal return was almost colorless and the results of the test were not influenced in any way by bile. There is no difference between the result in this case and that in the others.

3. Clark, W. M.: Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1925.

4. Benedict: J. Biol. Chem. 68:759, 1926.

CONCLUSIONS

The tables demonstrate that there is a direct proportion between the length of incubation and the amount of dextrose produced. In a few of the experiments, the rise was not entirely uniform, but it will be noticed that in every experiment the thirty minute tube is greater than the five minute tube and less than the sixty minute. The cause of this uneven rise seemed to be in the mixing of the solution when diluting it 1:600; in the last three experiments the solution was thoroughly mixed and the rise was uniform.

A weak dilution of enzyme is necessary for this demonstration, as an undiluted mixture will be strong enough to quickly hydrolyze the starch completely. Such a complete hydrolysis will form enough dextrose and maltose to more than reduce the amount of alkaline copper sulphate used. This was explained in the original article.

TABLE 2.—*The Effect of Incubation on the Power of Diastatic Enzymes in Duodenal Return to Convert Starch Into Sugar*

	Amount of Dextrose in milligrams								
Incubated Minutes	Experiments								
	4	5	6	7	8	9	10	11	12
5.....	71	83	55	71	114	69	114	125	95
10.....	67	79	60	89	77	91	174	133	125
15.....	77	97	54	80	...	111	210	143	154
20.....	...	103	60	89	236	100	265	200	182
25.....	262
30.....	117	111	60	98	282	125	365	225	223
35.....	133	400
40.....	180	149	71	108	286
60.....	143	143	91	167	393	500	334

COMMENT

There are a few other comments in Dr. Bassler's article that are worthy of consideration. In his conclusions, he makes the following general statement:

3. Dissociation of pancreatic enzymes does not occur in disorders and diseases of the gland. If amylopsin is deficient, there will also be a lack of trypsin.

In a former article I went into the work of various investigators at some length, and presented phases of their work that made me think that such a dissociation did not occur, in spite of some evidence that a few of these men advanced. However, there is no proof that dissociation of enzymes is an impossible state of affairs. Perhaps Dr. Bassler has the facts at hand to warrant this "ex cathedra" statement; I cannot find them in his article.

SUMMARY

If the pancreatic enzyme, diastase, is diluted sufficiently so that it does not hydrolyze starch too rapidly, it is possible to demonstrate a definite relationship between the length of incubation and the amount of starch hydrolyzed to dextrose or maltose.

THE ANTI-ASTHMATIC EFFICIENCY OF EPINEPHRINE, EPHEDRINE AND ATROPINE

THEIR COMPARATIVE EFFECTS ON A SERIES OF EXPERIMENTAL
ATTACKS IN A SUBJECT WITH A COMPLEX TYPE
OF ASTHMA *

O. W. BARLOW, PH.D.

AND

J. F. FRYE, M.D.

CLEVELAND

Observations on asthmatic persons, as well as on their reactions to drugs after the development of symptoms, have been made frequently, but we have not found any record of observations of a similar nature immediately preceding, during the development and course of, or during recovery from, an attack subsequent to the administration of a bronchodilating drug. Such an opportunity was afforded through the cooperation of one of us (J. F. F.). This subject, in whom uniform attacks could be reproduced by means of exercise (air hunger), offered the special advantage of testing the influence of the various anti-asthmatic drugs on the course of the attacks under controlled and comparable conditions.

EXPERIMENTAL WORK

The subject was a medical student, aged 27. The asthmatic tendency was first noticed at the age of 19. The history and physical examination on entrance to the medical school showed nothing abnormal. During the course of the study, which was carried out at intervals during the second, third, and fourth years, he was approximately 10 Kg. overweight according to the usual standards, but was normal for his physical type. No foci of infection could be detected, and the physical examination was negative except for the observation of a slightly deflected nasal septum, the significance of which will be discussed later.

The type of asthma presented was complex, i. e., primarily allergic, as a certain kind of dust invariably precipitated an attack, but was partly reflex, as the presence of an irritant in the air passages with subsequent sneezing, as well as air hunger as a result of strenuous exercise, almost invariably produced bronchial changes with emphysema and typical more or less acute asthmatic attacks as sequelae. These sympto-

* Submitted for publication, Sept. 12, 1929.

* From the Department of Pharmacology of the School of Medicine, Western Reserve University.

matic conditions differed in no respect from the usual allergic responses and persisted for at least eight hours after development (longer observations were not made before relieving the condition), and were promptly relieved by epinephrine.

Methods.—The criteria used for ascertaining the presence and the course of the asthmatic attacks were the subjective symptoms, the respiratory movements and volume, and the degree of emphysema present. Records of the volume of the chest and the respiratory excursions while the subject was in a reclining position were obtained by means of a pneumograph and tambour, the recording lever of which registered the changes on a smoked drum. A record showing the effects of an asthmatic attack induced by exercise on the respiratory rate and volume is illustrated by the tracing in figure 1. In the initial experiments the respiratory minute volumes were likewise recorded, but owing to the added discomfort these observations were discontinued. In a few directional tests, the respiratory rate, minute volume, tidal air volume, vital capacity, alveolar carbon dioxide, heart rate, stroke volume and blood pressure were determined under normal conditions after the development of an attack and following the subcutaneous administration of epinephrine.

Records were obtained during asthmatic attacks that developed under normal conditions; i. e., allergic, as well as reflex due to sneezing, and before, during and after the symptomatic treatment of attacks precipitated by means of air hunger following short periods of strenuous exercise such as hopping in place. The various measures tested for the purpose of giving symptomatic relief included the subcutaneous administration of epinephrine, ephedrine sulphate or atropine sulphate and the surgical correction of the deflected nasal septum. The influence of ephedrine administered orally or subcutaneously and of epinephrine subcutaneously as required for relief from attacks was observed during the entire three year period of study.

Results.—In the table are shown the respiratory rate, minute volume, tidal air, vital capacity, alveolar carbon dioxide, blood pressure and heart rate before, during and after relief obtained by means of epinephrine from an attack of asthma developed by air hunger. The most significant changes noted during the attack were those of respiration, i. e., rate, tidal air and vital capacity. The respiratory rate increased markedly, recovered partially on cessation of the exercise and assumption of the prone position, but remained much above normal. The tidal air volume was reduced 30 per cent but was compensated for by an increased minute volume. The vital capacity was reduced from a normal value of 4,100 cc. to 1,500 cc. (a decrease of 63 per cent) during the attack, with a resulting increased dead space and the development

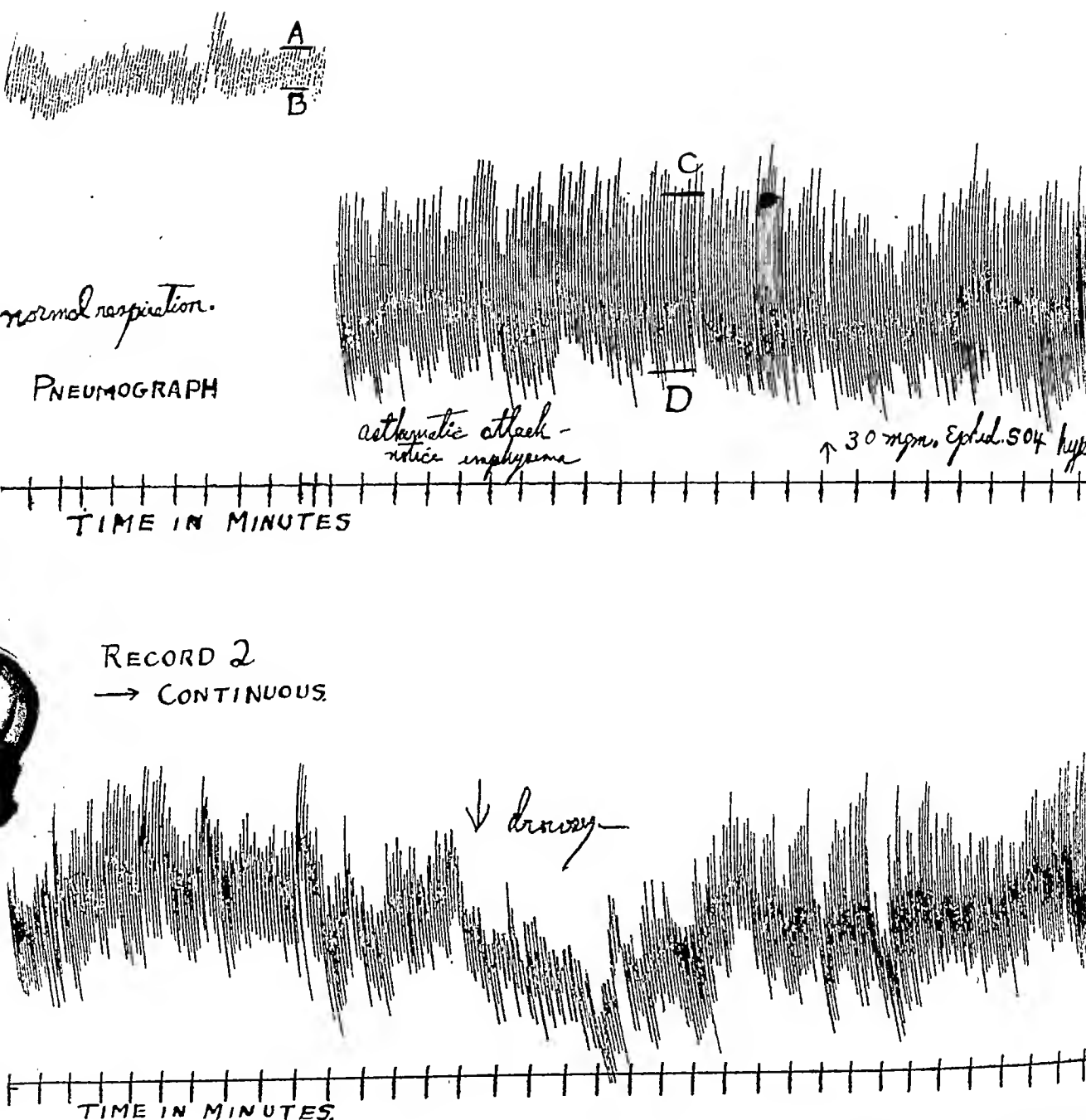
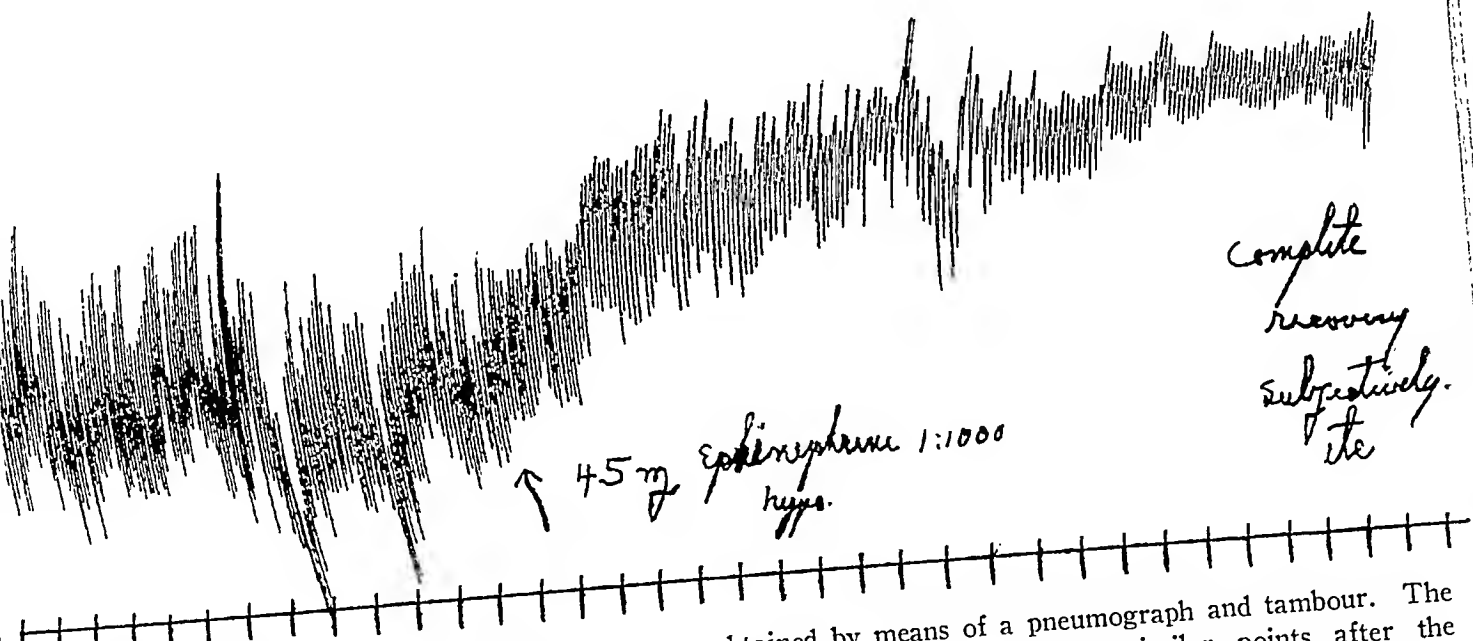
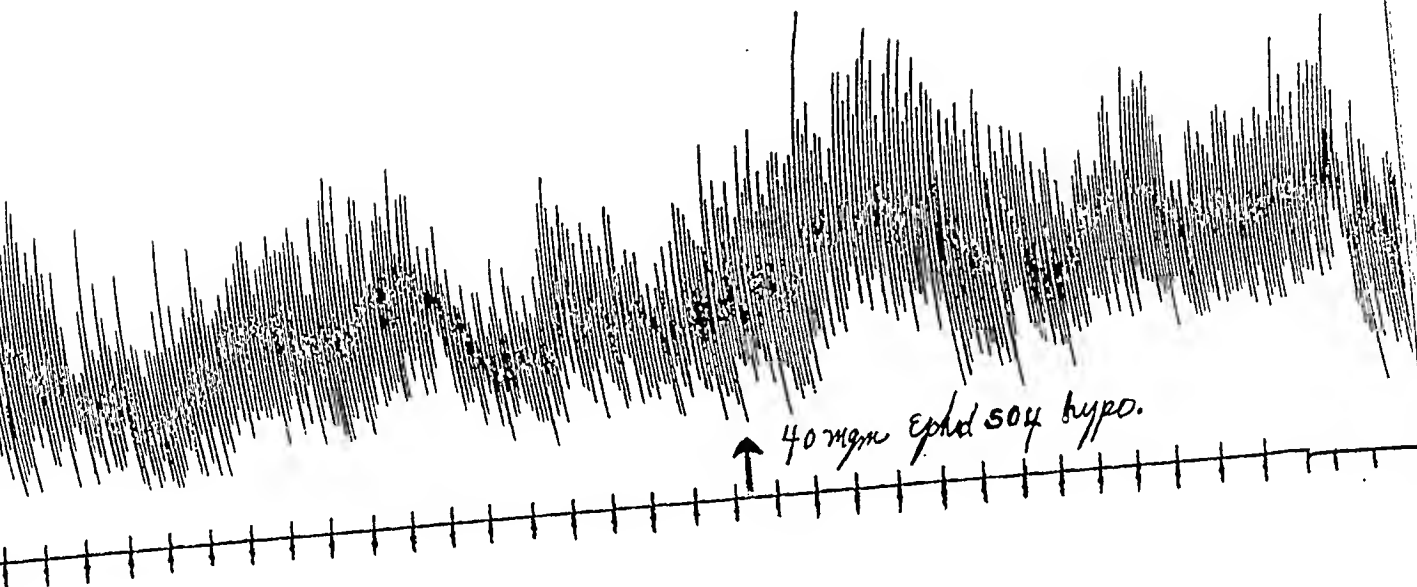


Fig. 1.—The influence of ephedrine on an acute attack of asthma. Reproduction of a type experiment. The upstroke of the lever recorded the expiratory movement. The letters *A* and *B* represent the limits of normal respiration, and *C* and *D* represent the limits of development of asthma.

RECORD 1.



complete
recovery
subjectively.
etc

showing the respiratory movements and volumes obtained by means of a pneumograph and tambour. The the expiratory and inspiratory phases under normal conditions; C and D, similar points after the

of emphysema. The alveolar carbon dioxide readings obtained during the attacks were apparently normal, but it is doubtful whether the values noted during the attack were correct, as the type of breathing pointed to an increased carbon dioxide tension and it is quite probable that under the conditions, a true alveolar sample was not obtained. The circulatory changes were compensatory and of secondary importance. On administration of epinephrine, subjective relief was apparent within one minute, and symptomatic recovery was generally complete within from six to ten minutes, as is shown by the respiratory data in the accompanying table.

*The Influence of Epinephrine * on the Symptoms of an Induced Asthmatic Attack*

Observations	Normal	During Attack	Administration of Epinephrine		Comment
			2 Minutes Later	10 Minutes Later	
Temperature.....	37.2 C. (98.9 F.)	37.2 C. (98.9 F.)	37.4 C. (99.3 F.)	37.2 C. (98.9 F.)	
Respiration rate.....	18	28	21	19	
Tidal volume.....	500 cc.	350 cc.	725 cc.	545 cc.	
Minute volume.....	9,000 cc.	9,800 cc.	15,225 cc.	10,355 cc.	
Vital capacity.....	4,100 cc.	1,500 cc.	4,400 cc.	4,300 cc.	
Alveolar CO ₂	3.9%	3.9%†	3.9%	3.9%	
Blood pressure.....	104/70	130/84	122/72- 118/60	112/65	Dyspnea, emphysema
Heart rate.....	77	100	99	84	Counted
Time of entire systole.....	0.27 seconds	0.24 seconds	0.23 seconds	0.25 seconds	Optical records
Time of entire diastole....	0.608	0.36-0.40	0.33-0.31	0.43 seconds	Optical records
Total cycle.....	0.875	0.6 -0.64	0.56-0.54	0.78	Optical records
Delay at rise.....	0.12-0.11	0.1 -0.095	0.12-0.11	Optical records
Delay at incisura.....	0.12-0.11	0.1 -0.10	0.125-0.11	Optical records
Velocity of pressure wave.	5.04 m./sec.	5.8 m./sec.	6.8 m./sec.	5.04 m./sec.	Optical records

* The dose was 5 minims (0.3 Gm.) of a 1:1000 solution.

† Figure given is not reliable.

A comparison of the efficiency of epinephrine, ephedrine and atropine in relieving the changes in respiratory rates, volumes and grossly the degree of emphysema produced by an asthmatic attack developed by air hunger is shown in figure 2. Each curve represents the median observation from several experiments of the same type. The figure was constructed by plotting the median measurements of the actual changes observed in the several experiments on the time of action. (The actual records as illustrated by figure 1 inverted, as the lever moved downward during inspiration; i. e., figure 2 *B* would correspond roughly to figure 1 if the latter were turned upside down and read from right to left.)

The contrast between the efficiency of epinephrine and ephedrine as to the time of action in giving symptomatic relief from an induced asthmatic attack was striking. The administration of epinephrine gave symptomatic relief, which was apparent within from thirty to sixty seconds and was reflected by the rapid disappearance of the choking sensation and emphysema, as illustrated by the prompt return of the

respiratory phases toward normal (fig. 2 *A*, *B* and *C*). The profuse sweating due to the dyspneic breathing subsided after two or three minutes, and after a short compensatory increased ventilation due probably to an increased alveolar carbon dioxide tension (developed during the attack), recovery was complete.

The subcutaneous administration of ephedrine sulphate in from 45 to 75 mg. doses was followed, in the majority of the tests, by a slow but

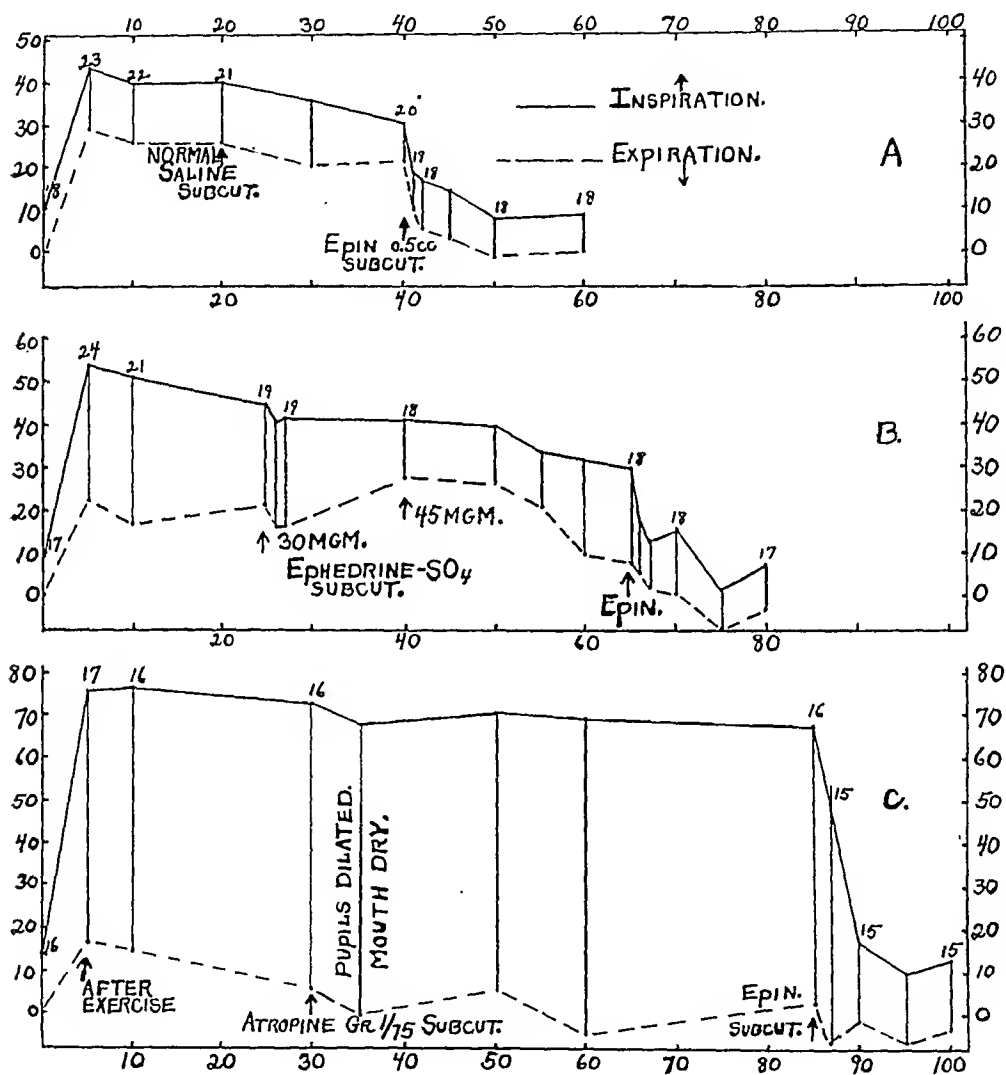


Fig. 2.—Graphic comparison of the efficiency of epinephrine, ephedrine and atropine on the course of a series of asthma reactions induced by exercise. Each curve represents the median of a series of experiments and was constructed by inverting the measured changes which developed as illustrated in figure 1, to show the alterations in the volume of the chest before and during an attack and after the administration of the respective drug. The numerals on the horizontal scale represent the respiratory rates per minute; those on the vertical scale, the change in the lever, by millimeters. *A* gives the median for five experiments; *B*, the median for four experiments and *C* the average of two experiments.

gradual alleviation of the symptoms. The ephedrine effect became evident after twenty-five minutes and extended over a forty to eighty minute period, as illustrated in figure 2 *B*. This likewise shows the rapid terminal recovery produced by epinephrine after a prolonged and incomplete ephedrine reaction.

The subcutaneous administration of $\frac{1}{75}$ grain (0.0008 Gm.) of atropine sulphate did not give relief from the symptoms during the fifty-five minutes succeeding the development of an attack, as shown in figure 2 *C*, although the pupils were widely dilated and the mouth became very dry within from four to seven minutes after the administration of the drug. This curve therefore, in the absence of any antiasthmatic action of atropine under the conditions of the experiment, may be utilized to illustrate the persistence over ninety minutes of asthmatic attacks which developed as a result of air hunger. Longer graphic records have not been obtained although subjectively attacks have persisted for eight hours, at which time epinephrine was necessary for relief.

The surgical correction of the deflected nasal septum did not significantly influence either the number or the severity of the allergic or reflex asthmatic attacks during the year following the operation.

The use of epinephrine, ephedrine or atropine for relief from the symptoms of asthma during the entire three year period indicates that the efficiency of these drugs, as judged from the degree of relief afforded, was quite similar to that noted with the induced attacks, as illustrated in figure 2. Epinephrine was the most effective, i. e., gave prompt relief in both mild and acute attacks. Atropine was the least effective of the drugs tested and was discontinued on account of undesirable action on the eye and salivary secretions. Ephedrine administered subcutaneously as a 3 per cent solution or taken orally in capsule form in from 45 to 90 mg. doses was effective in limiting the number of attacks or in alleviating mild attacks. Relief, however, required the prompt administration of one or two capsules daily on the first appearance of symptoms and for several days thereafter. In acute attacks, ephedrine was practically ineffective, as shown in figure 1, although all symptoms under such conditions, even after the ineffective administration of ephedrine, were promptly relieved by epinephrine.

The degree of effectiveness of ephedrine as noted in this series of studies is in agreement with those of numerous recent publications. Leopold and Miller,¹ in reviewing a mixed series of fifty-nine cases of asthma, observed that the drug gave complete relief in 56 per cent,

1, Leopold, S. S., and Miller, T. G.: Use of Ephedrine in Bronchial Asthma and Hay-Fever, *J. A. M. A.* **88**:1782 (June 4) 1927.

partial relief in 29 per cent and no relief in 15 per cent of all cases tested. Complete relief was obtained in all cases of the anatomic or reflex nasal type; 84 per cent of the cases of the allergic type reacted completely, while only 38 per cent of the infectious type showed complete relief. Corresponding observations were obtained by Munns and Aldrich,² on a series of 22 unselected cases. Stewart,³ maintained that the therapeutic use of ephedrine in the treatment for asthma should be further limited, in that its chief use seems to be as a preventive; that is, it reduces the frequency and severity of the attacks in mild or chronic asthmatic conditions, while in acute attacks of either the simple or complex type, it is ineffective.

CONCLUSIONS

1. The asthmatic respiratory and circulatory changes are described which occur in a subject who is able to induce a typical attack of asthma by means of exercise.

2. During these induced attacks, the movements and volume of the chest were recorded by means of a pneumograph tambour arrangement. This method was utilized for comparing the efficiency of several antiasthmatic drugs.

3. Studies of the antiasthmatic efficiency of epinephrine, ephedrine and atropine on the course of comparable induced attacks of asthma as well as the routine use of these drugs in producing relief from allergic or reflex attacks over a three year period showed that the efficiency of these drugs from greatest to least was in the order named; i. e., epinephrine was effective in all attacks; ephedrine was most effective in relieving mild attacks or as a preventive, while atropine was unsatisfactory for either acute or mild attacks.

2. Munns, G. F., and Aldrich, C. A.: Ephedrine in Treatment of Bronchial Asthma in Children, *J. A. M. A.* **88**:1233 (April 16) 1927.

3. Stewart, H. H.: *Brit. M. J.* **1**:293, 1929.

INSULIN INACTIVATION BY HUMAN BLOOD CELLS AND PLASMA IN VITRO

EFFECT OF NORMAL AND OF DIABETIC BLOOD ON INSULIN ACTION *

SAMUEL KARELITZ, M.D.

PHILIP COHEN, M.D.

AND

SIDNEY D. LEADER, M.D.

NEW YORK

Patients suffering from diabetes mellitus are known to have periods during which they do not respond properly to insulin. It is likewise well established that diabetes becomes worse during infection, injury or operation. These observations have aroused much interest and investigation in the past few years. It is interesting that seventy-five years ago Claude Bernard¹ was well aware of the danger of infection to diabetic patients.

Patients who temporarily or permanently resist insulin action are called insulin resistant or insulin refractory. The periods of resistance to insulin may be recurrent, ending in spontaneous recovery, or may be lasting, terminating in coma and death.

In July, 1925, E. K., a girl, aged 6 years, with severe diabetes, began to have peculiar reactions to insulin. On a constant diet and without any evident complication, she seemed to resist insulin action at one time and at another to have hypoglycemia on the same or smaller dosage of insulin. This was temporary and no infection was found. Dr. B. Schick suggested that this child might have a substance in her blood that inhibited insulin action.

By tests on rabbits we found that the patient's blood did affect insulin action. At the same time we were surprised at finding that normal blood, used as a control, also inhibited insulin action. The relative effect of normal and diabetic blood on insulin action is represented by the blood sugar determinations made before injection and hourly for three hours after the subcutaneous injection of the blood-insulin mixture into rabbits. It is evident that the diabetic blood was much more effective in preventing the action of the insulin than was the normal blood (table 1).

* Submitted for publication, Sept. 12, 1929.

* From the Departments of Pediatrics and Laboratories of Mount Sinai Hospital.

* A preliminary report of this study was published in *Proc. Soc. Exper. Biol. & Med.* **26:11**, 1928.

1. Bernard, Claude, quoted by Mauriac, P., and Aubertin, E.: *Presse méd.* **34:1633** (Dec.) 1926.

The figures in table 1 show clearly that 1.5 cc. of blood plasma from a diabetic or normal human being was inadequate to affect the blood sugar, but that 5 cc. of either plasma was sufficient to have a definite effect.

After the aforementioned observations had been made, numerous problems presented themselves, of which the following were studied:

1. Does the blood plasma of all human beings inactivate insulin *in vitro* and is it a quantitative reaction? 2. Do blood cells have the ability to inactivate insulin? 3. Is this reaction always greater with the blood of diabetic patients? 4. Are dilution of the mixture, viscosity, slow absorption or p_H change factors in inhibition by blood? 5. Do white blood cells or pus have greater power of inactivation than blood plasma or ordinary blood cells? 6. Is this inactivation greater during spontaneous infection or during artificially produced diseases simulating infection, such as serum sickness or phase after vaccine injection? 7. What are some of the properties of this inhibitory substance in the blood? Is it affected by heat, cold or p_H change; is the time of incubation a factor?

TABLE 1.—*Blood Plasma*

	Blood Plasma	0 Hours	1 Hour	2 Hours	3 Hours
E. K., diabetic.....	1.5 cc.	0.090	0.045	0.040	Convulsions
	5 cc.	0.115	0.095	0.093	0.090
Normal.....	1.5 cc.	0.102	0.055	0.050	0.056
	5 cc.	0.095	0.071	0.056	0.082

PROCEDURE

Unless otherwise stated, all studies were made as follows: The substance investigated (usually blood plasma or cells) was mixed with 3 units of Lilly's or Squibb's insulin which was diluted with physiologic solution of sodium chloride so that 1 cc. contained 1 unit of insulin. The mixture was usually made up to 10 cc., with physiologic solution of sodium chloride incubated at 37 C. for one hour; it was then injected subcutaneously into rabbits weighing 2 Kg., which were starved for the preceding twenty-four hours. For sugar determinations, blood was obtained from the marginal vein of the ear before injection and hourly for three hours afterward. Blood cells were obtained by centrifugation of citrated blood for fifteen minutes at high speed. They were not washed except in a few experiments used for comparison. Blood sugar determinations were made by the micromethod of Folin-Wu as modified by T. Kuttner.² Sugar determinations were done singly and were repeated on the filtrates when necessary.

EXPERIMENTAL DATA

The results of our experiments are presented in composite curves. Each point represents the average of several similar experiments which are presented singly in the succeeding tables. Throughout the ordinate

2. Kuttner, T.: Personal communication to the authors. The method is to be published.

TABLE 2.—Control Experiment on the Blood Sugar of Rabbits, Showing the Effect of Subcutaneous Injection of Three Units of Insulin Previously Incubated with Saline Solution for One Hour at 37 C.

Blood Sugar in Milligrams Before Injection	Blood Sugar in Milligrams After Injection			
	1 Hour	2 Hours	3 Hours	
98	62	58	..	Convulsion 2 hours
80	50	Convulsion 1¾ hours
84	58	47	..	Convulsion 2¾ hours
110	66	66	66	
102	65	Convulsion ½ hour
112	66	44	..	Convulsion 1¾ hours
113	72	40	..	Unsteady
111	54	43	..	Convulsion 2¼ hours
100	74	52	43	Convulsion 3 hours
92	62	44	38	
118	81	70	70	
85	62	58	68	Unsteady
75	45	45	40	Unsteady
66	66	55	44	Unsteady
92	66	70	50	Convulsion 2½ hours
83	44	44	44	
110	55	58	..	Convulsion 2 hours
112	58	58	..	Convulsion 2 hours
105	51	42	40	
108	56	50	..	Convulsion 2 hours
110	72	55	46	Unsteady
114	50	50	..	Convulsion 2 hours
110	55	50	50	Convulsion 2½ hours
Average	92	51	45	

TABLE 3.—Studies on Rabbits with Normal Blood Plasma and Control, Showing the Effect of the Subcutaneous Injection of Various Amounts of Human Blood Plasma Previously Incubated at 37 C. for One Hour with Three Units of Insulin

Amount of Plasma	Milligrams of Blood Sugar				
	Before Injection	After Injection			
		1 Hour	2 Hours	3 Hours	
15 cc.	112	110	110	106	Irritable
	100	100	100	102	
10 cc.	103	88	70	86	
	120	96	65	82	
	63	66	66	66	
	77	73	72	73	
	99	92	81	83	
	90	61	66	70	
	78	75	75	75	
	95	85	85	88	
	92	80	85	87	
	98	85	72	78	
	94	86	78	75	
	98	82	85	80	
100	85	72	70		
94	86	82	90		
Average.....	93	81	75	79	
5 cc.	95	71	56	82	
	83	66	64	53	
	97	70	61	55	
	94	75	71	57	
	94	68	55	75	
	98	76	65	75	
Average.....	93	73	66	69	
4 cc.	90	72	88	90	
	101	92	62	65	
	88	74	70	72	
3 cc.	95	60	49		
	115	75	46	40	
2 cc.	90	72	60	66	
	94	55	50	52	
	91	52	42	48	
1 cc.	102	55	50	49	
	105	56	52	58	
	90	65	40	49	
				Convulsions 150 min.	

represents the sugar content of the rabbit in milligrams per hundred cubic centimeters of blood and the abscissa the time of determination, which always was before injection or at zero, and one, two and three hours after injection.

Chart 1 shows that the control group acted as was expected. Most of the animals developed marked hypoglycemia in one hour, which became more marked in the second and third hours. Eighteen of the twenty-five rabbits had convulsions. The convulsions nearly always

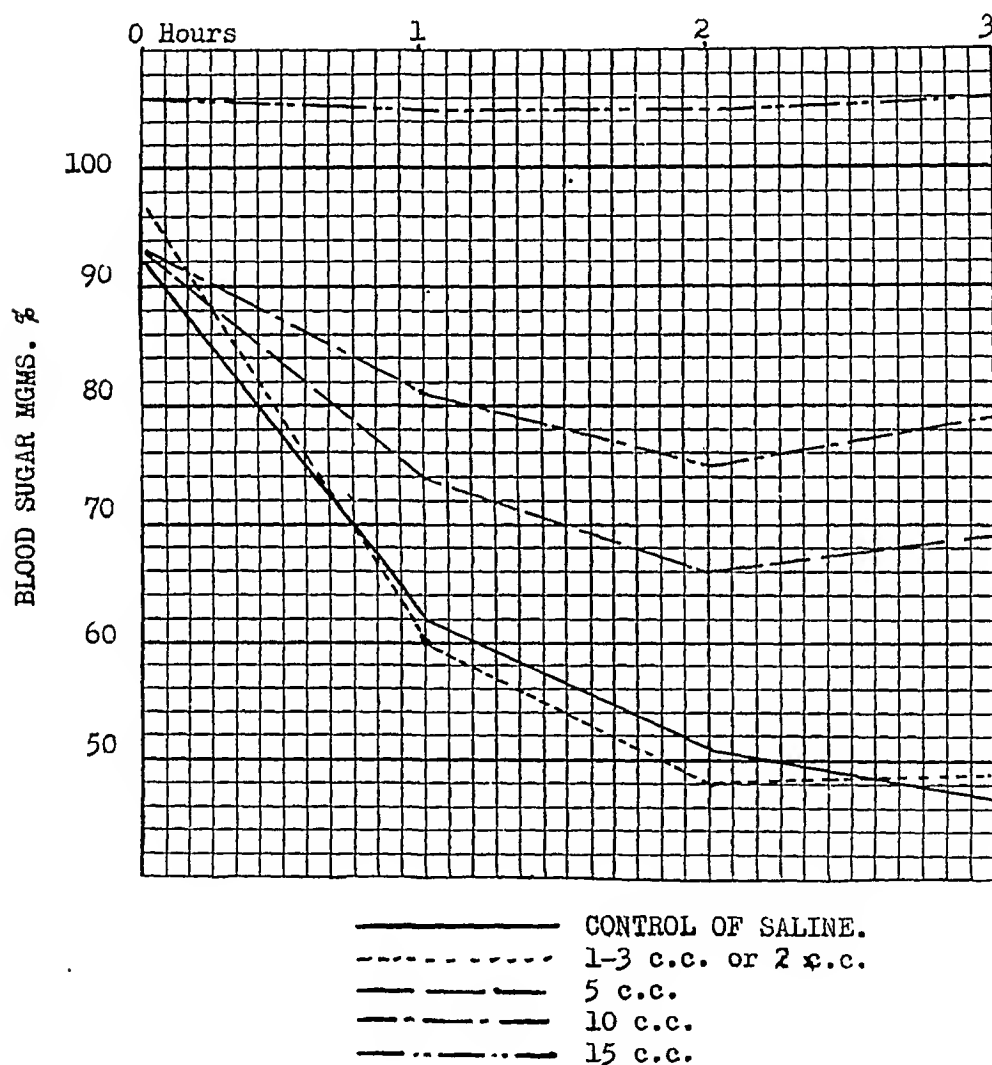


Chart 1.—The effect of various amounts of blood plasma on insulin action.

ceased and hypoglycemia was relieved within five minutes by the subcutaneous injection of dextrose solution.

When 1, 2 or 3 cc. of blood plasma was mixed with 3 units of insulin and injected, the blood sugar dropped almost as low as in the control rabbits, but convulsions were rarely observed. When 4 or 5 cc. of blood plasma was used, the usual insulin action was inhibited. When 10 cc. of blood plasma was used, almost complete

neutralization of the insulin action occurred, and with 15 cc. hardly any change in blood sugar could be noticed.

It is evident that not all rabbits responded in exactly the same way to any one procedure. That is probably due to a variation in individual reaction. By comparison with a number of similar experiments, however, a correct impression can be obtained.

TABLE 4.—*Experiment on Blood Sugar of Rabbit, Showing the Effect of the Subcutaneous Injection of Various Amounts of Human Blood Cells Previously Incubated at 37 C. for One Hour with Three Units of Insulin*

Amount of Cells	Blood Sugar in Milligrams			
	Before Injection	After Injection		
		1 Hour	2 Hours	3 Hours
5 cc.	97	98	92	92
	104	85	65	45
	100	84	82	76
	104	86	68	72
	115	110	108	100
	114	84	86	84
	96	75	65	65
	82	40	55	80
	87	52	70	82
	108	82	92	90
	92	80	88	90
	90	77	80	80
	90	64	67	70
	103	92	98	98
	96	94	94	95
	114	110	98	100
	90	100	92	90
	95	80	75	70
Average....	98	78	81	82
3 cc.	90	75	70	70
	90	58	55	60
	92	65	70	75
	90	85	80	80
2 cc.	88	64	52	56
	96	80	70	66
	94	55	35	..
	94	74	40	..
	98	55	40	..
	106	90	80	76
	116	60	55	64
	108	55	55	55
	105	65	55	65
	95	60	68	..
	92	58	64	60
	88	58	60	50
	86	50	50	..
	Average....	98	65	62

Convulsions 2 hours
Convulsions 2 hours
Convulsions 2 hours

Convulsions 2 hours
Convulsions 2 hours

Effect of Blood Cells on Insulin Action.—It was our impression that the inactivation of insulin was probably due to an enzyme-like substance. If this was true, blood cells, especially leukocytes and pus cells, should have a greater inhibitory effect on insulin action by virtue of their greater enzyme content.

The composite curve (chart 2) and tables 4 and 5 show that 5 cc. of blood cells gave the same reaction as 10 cc. of plasma and 3 cc. of blood cells that of 5 cc. of plasma. Although 2 cc. of cells was inadequate to cause much insulin inactivation, it was enough to make a definite inhibitory impression. Yet no consistent reaction was obtained with blood cells. It was therefore decided to lake the cells. Washed blood cells used as controls acted as did the unwashed cells.

TABLE 5.—*Experiments on the Blood Sugar of Rabbits, Showing the Effect of Laked Human Blood Cells Previously Incubated for One Hour with Three Units of Insulin at 37 C.*

Amount of Cells	Blood Sugar in Milligrams				
	Before Injection	After Injection			
		1 Hour	2 Hours	3 Hours	
Laked Blood Cells					
5 cc.	103	92	98	98	
	96	84	94	95	
	114	110	88	100	
	90	100	92	90	
	92	92	90	95	
3 cc.	95	94	92	95	
	96	95	95	102	
2 cc.	102	94	90	90	
	98	96	98	90	
	97	95	87	96	
	93	80	75	90	1/2 hour incubation
	85	89	70	80	1/4 hour incubation
	94	92	94	94	1/2 hour incubation
	92	85	92	88	1/8 hour incubation
	92	92	92	90	1/2 hour incubation
	90	93	92	95	1/8 hour incubation
	Average.....	95	92	90	92
1 cc.	92	82	78	75	
	88	75	70	76	
	93	76	72	75	
	102	90	75	70	
0.5 cc.	92	55	64	65	
	92	60	60	68	
	96	55	62	70	
	92	55	60	68	
	95	50	72	78	
	97	60	65	70	
Washed Laked Blood Cells					
2 cc.	102	98	102	100	
	94	90	88	90	
1 cc.	95	85	90	92	
	98	82	80	95	

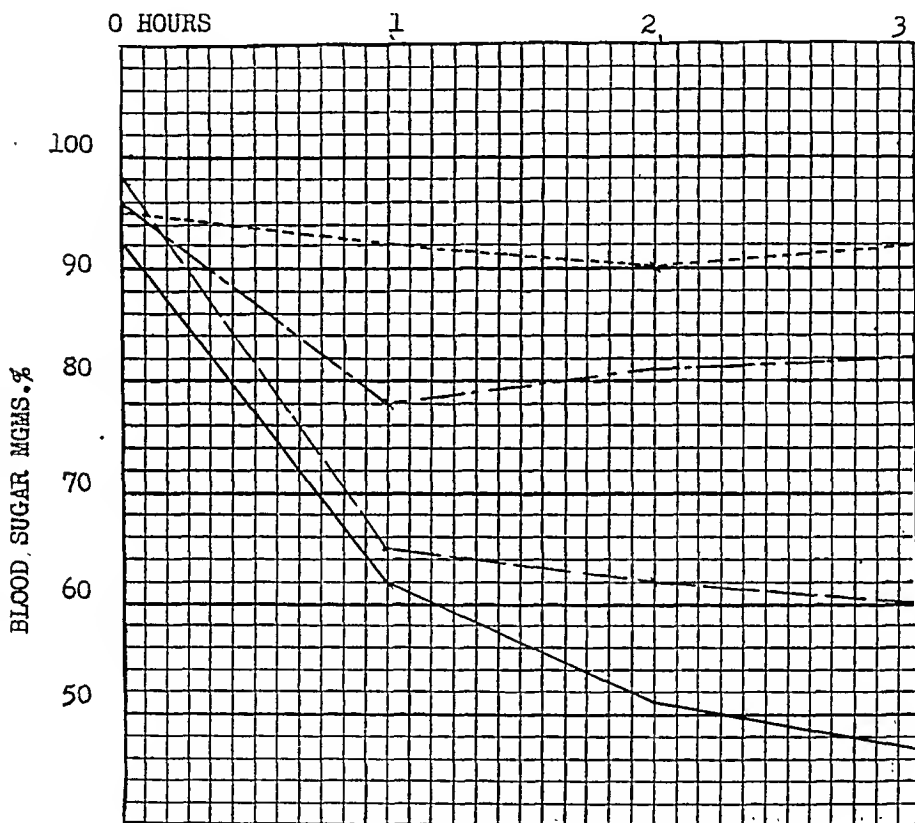
The blood cells were then laked with distilled water and a marked difference was observed. Two cubic centimeters of laked cells regularly caused complete neutralization, even more than did 10 cc. of plasma or 5 cc. of unlaked cells. One cubic centimeter of laked cells was more inhibitory than was 5 cc. of plasma or 3 cc. of cells intact. As little as 0.5 cc. of laked cells caused definite inhibition. It is therefore fairly evident that this inhibitory substance is mainly intracellular.

Effect of Diabetic Blood on Insulin Action.—After it had been demonstrated that the blood of patient E. K. had greater inhibition of the

insulin action, we compared other diabetic bloods with those of normal persons. The experiments in table 6 show the striking difference in the power of inhibition of insulin action existing between diabetic and nondiabetic blood.

Before speculating on an explanation of this observation, various controls were necessary to rule out the significance of dilution, viscosity of the blood or p_H of the blood (chart 3).

The question of dilution is answered by the many saline controls, in which 3 units of insulin was diluted to 10 cc. with physiologic solution



EFFECT OF BLOOD CELLS ON INSULIN ACTION

— CONTROL OF SALINE
 - - - - 5 c.c. NORMAL BLOOD CELLS
 — — — 2 c.c. NORMAL BLOOD CELLS
 - - - - 2 c.c. NORMAL LAKED CELLS

Chart 2.—The effect of blood cells on insulin action. The continuous line represents the control of saline; the long dash dot line, 5 cc. of normal blood cells; the long dash line, 2 cc. of normal blood cells, and the short dash line, 2 cc. of normal laked cells.

of sodium chloride. The results were similar to those seen from insulin alone. Agar-agar and egg albumin were used to study the questions of viscosity and adsorption. Here again the results were similar to those due to insulin alone.

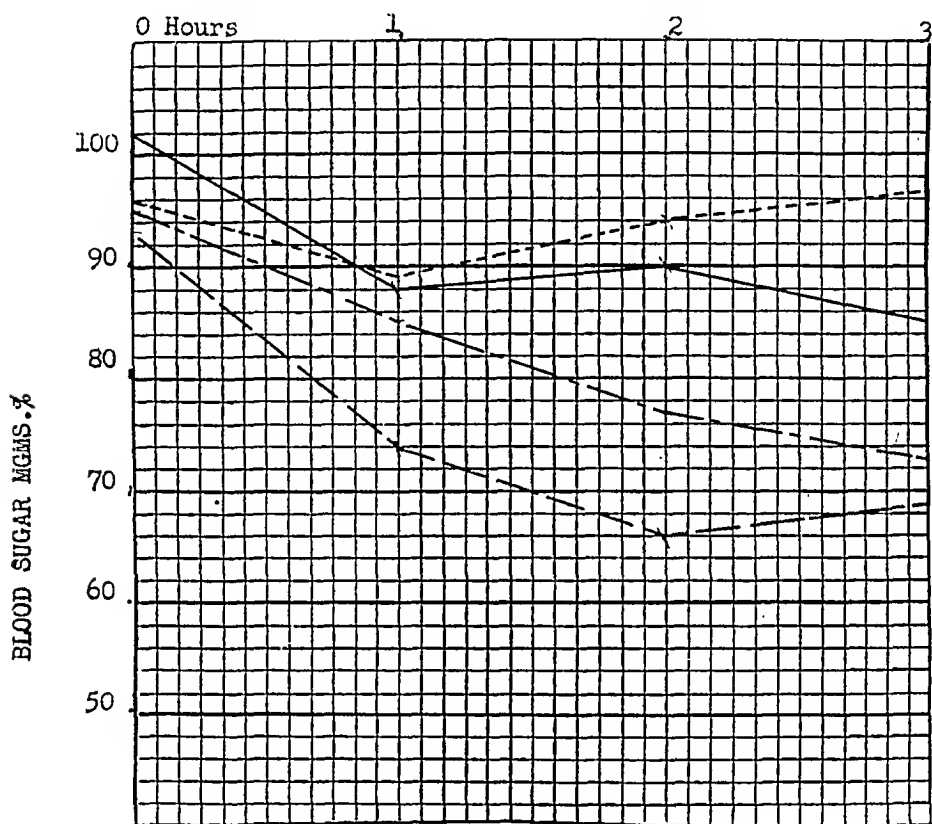
TABLE 6.—*Rabbit Blood Sugar Curve, Showing the Effect of the Subcutaneous Injection of Various Amounts of Blood Cells of a Diabetic Patient Previously Incubated at 37 C. for One Hour with Three Units of Insulin*

Amount of Cells	Blood Sugar in Milligrams			
	Before Injection	After Injection		
		1 Hour	2 Hours	3 Hours
5 cc. of plasma or serum	115	95	93	90
	122	83	80	83
	85	85	85	85
	85	75	80	70
	95	85	85	80
	90	80	80	80
	108	110	94	90
	105	105	110	102
	105	100	100	95
	112	80	80	78
	105	66	104	100
5 cc. of cells.....	95	88	84	80
	110	105	100	96
	102	85	95	95
	105	80	88	80
3 cc. of cells.....	90	75	75	65
	95	73	75	70
2 cc. of cells.....	88	64	52	56
	98	78	75	68
	102	78	68	65
	112	76	64	68
	98	75	58	60
	106	77	62	70
	112	70	60	56
	110	62	50	50
	105	64	60	55
Laked Diabetic Blood Cells				
2 cc. of cells.....	94	98	95	97
	96	95	95	95
1 cc. of cells.....	101	105	100	102
	92	90	92	95
	92	86	92	94
	99	74	91	95
0.5 cc. of cells.....	96	65	75	88
	91	76	84	86

TABLE 7.—*Control Experiments*

Amount of Cells	Agar-agar					
	Before Injection	After Injection				
		1 Hour	2 Hours	3 Hours		
Agar-agar						
4 cc.	115	56	55	..	Convulsions 2 hours	
6 cc.	112	55	55	..	Convulsions 2 hours	
10 cc.	120	52	53	..	Convulsions 2 hours	
	115	54	54	..	Convulsions 2 hours	
Egg Albumin						
6 cc.	102	62	42	40	Convulsions	
8 cc.	108	58	46	40	Convulsions 2 hours	
10 cc.	112	60	48	40	Convulsions	
	107	60	45	40	Convulsions 2 hours	
Purified Horse Serum						
5 cc.	98	52	38	58	Convulsions	
	94	48	50	50	Irritable	
	96	50	48	48	Convulsions	
	94	50	60	42	Convulsions	

The question of p_H was more difficult to solve. It is known that insulin deteriorates in the presence of sodium and potassium hydroxide,³ and becomes inactivated by an alkaline buffer mixture.⁴ Its activity cannot be restored after destruction with sodium or potassium hydroxide, but can be restored by acidification with hydrochloric acid, after it has been inactivated by weak alkalis, as ammonium carbonate or ammonium hydroxide. Insulin becomes inactivated by alkali at p_H 7.2 or more



EFFECT OF DIABETIC BLOOD ON INSULIN ACTION

- 5 c.c. DIABETIC PLASMA
- 5 c.c. NORMAL PLASMA
- - - - - 1 c.c. CELLS LAKED DIABETIC
- . - . - 1 c.c. NORMAL LAKED CELLS

Chart 3.—The effect of diabetic blood on insulin action. The continuous line represents 5 cc. of diabetic plasma; the long dash line, 5 cc. of normal plasma; the short dash line, 1 cc. of laked diabetic cells, and the long dash dot line, 1 cc. of normal laked cells.

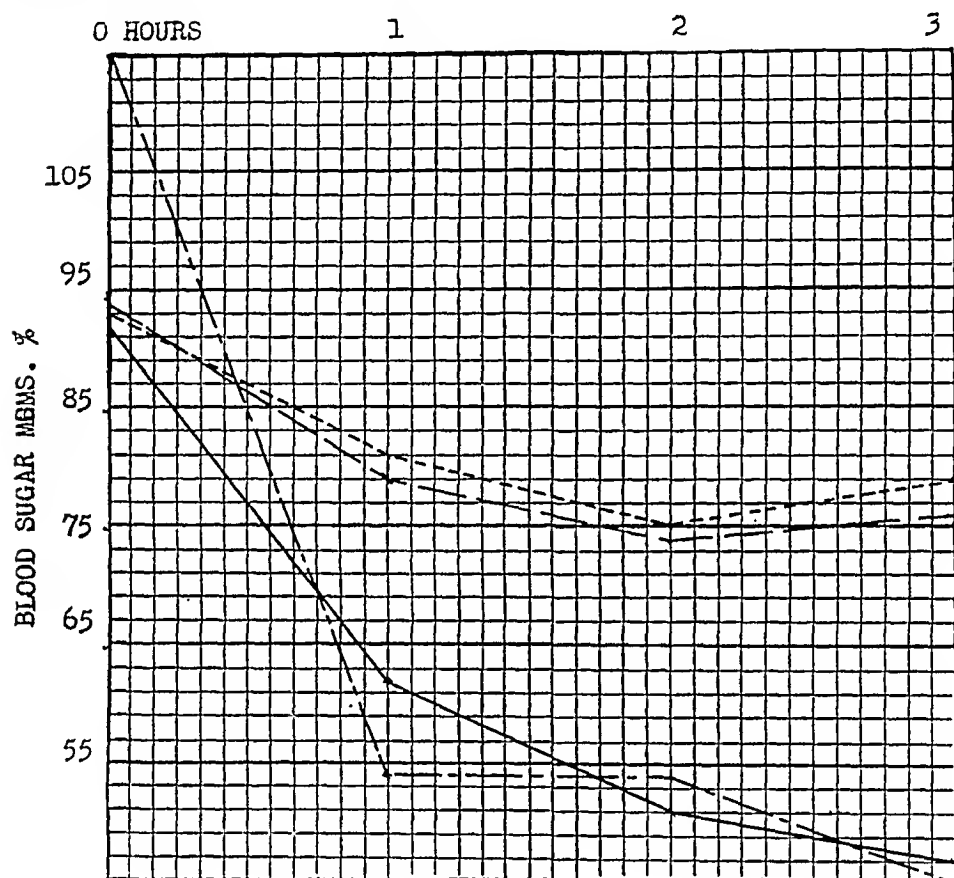
after many hours of incubation. Blood, after standing and being citrated, changes to a p_H of from 7.8 to 8.4. Our experiments were first to citrate blood which had been standing back to p_H 7.4 by the

3. Witzeman, E. J., and Livshis, L.: J. Biol. Chem. **58**:463 (Sept.) 1923.

4. Shonle, H. H., and Waldo, J. H.: J. Biol. Chem. **66**:467 (Dec.) 1925.

addition of tenth-normal hydrochloric acid. After that had been done, the usual insulin inhibition occurred.

If more insulin inhibition is to be expected because of the alkalinity at p_H 8, 5 cc. of blood plasma at that p_H might be expected to cause almost complete inhibition of 3 units of insulin. When 5 cc. of blood plasma at p_H 8 was tried, the effect on insulin was not unlike that obtained with 5 cc. of plasma at p_H 7.4. It was less than the inactivation



CONTROL EXPERIMENTS

- 10 c.c. SALINE
- - - - - 10 c.c. PLASMA
- 10 c.c. PLASMA PH. 7.40
- . - . - 4-6-10 c.c. GUM ARABIC

Chart 4.—Control experiments. The continuous line represents 10 cc. of saline; the short dash line, 10 cc. of plasma; the long dash line, 10 cc. of plasma with a p_H of 7.4, and the long dash dot line, 4, 6 and 10 cc. of gum arabic.

due to 10 cc. of plasma at p_H 7.4. Saline mixtures at from p_H 7.4 to 8 did not cause insulin inhibition, but at 9.2 mild insulin inactivation occurred. At p_H 6 blood plasma no longer inactivated the insulin. The p_H determinations were partly performed potentiometrically and partly by the La Motte colorimetric method. From these experiments, it seems

fairly clear that at the p_H of normal blood insulin is inactivated in vitro by human blood plasma, but that this inactivation is not due to the change toward alkalinity on standing; at p_H 6 this inhibitory substance is ineffective. The foregoing is true for the period of incubation used in our experiments—from one to two hours.

From chart 5 and table 8 it is evident that diabetic blood is much more inhibitory than normal blood. The reason for this is entirely speculative since the few suggestions which might be made here have not as yet been adequately proved. First we have to consider the conception of Epstein and Rosenthal,⁵ which is to the effect that in diabetes changed capillary permeability in the pancreas permits the passage of trypsin

TABLE 8.—*Effect of p_H on Insulin Activity*

Amount	Before Injection	After Injection			
		1 Hour	2 Hours	3 Hours	
10 cc. of serum at p_H 7.4.....	96	72	70	76	
	98	80	75	80	
	90	85	75	78	
	92	84	75	75	
	85	75	75	70	
10 cc. of serum at p_H 8.....	98	85	74	78	
	95	85	65	58	
5 cc. of serum at p_H 7.4.....	92	70	55	55	
5 cc. of serum at p_H 8.....	96	68	65	62	
	95	60	60	60	
10 cc. of serum at p_H 6.....	110	48	40	..	Convulsions
	106	45	38	..	Convulsions
	89	50	40	30	Convulsions
	92	62	50	40	Convulsions
10 cc. of p_H 6 after incubation one hour at p_H 8.....	84	78	55	55	
10 cc. of saline at p_H 6.....	96	67	36	33	Convulsions
10 cc. of saline at p_H 7.4.....	102	58	42	30	
10 cc. of saline at p_H 8.....	104	62	40	26	
10 cc. of saline at p_H 8.2.....	94	35	40	..	Convulsions
10 cc. of saline at p_H 8.6.....	90	62	60	55	
	80	60	50	35	
10 cc. of saline at p_H 9.2....	92	72	64	60	

into the blood stream, thus causing a comingling of the external and internal secretions of the pancreas. Epstein has shown that trypsin, in vitro, possesses power of rapidly neutralizing insulin under favorable conditions of hydrogen ion concentration.

In applying this idea here, we must assume that insulin inactivation by normal blood is due to trypsin, the concentration of which is increased in diabetes, thus accounting for the great inhibitory effect of the diabetic blood.

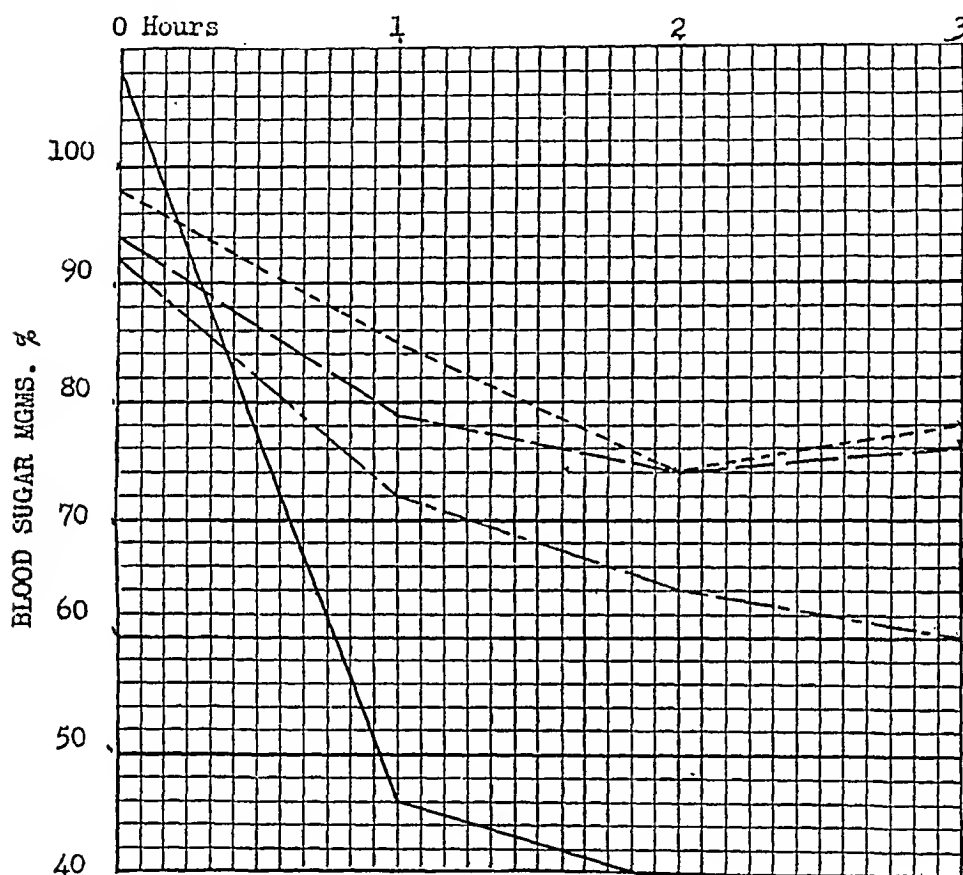
If we are to use Loewi's⁶ work to explain our observation, a liver product or glycamin is present in diabetic blood which inactivates the

5. Epstein, A. A., and Rosenthal, N.: Am. J. Physiol. **70**:225, 1924; **71**:316 (Jan.) 1925.

6. Loewi, O.: Klin. Wchnschr. **6**:2169 (Nov. 12) 1927.

insulin. Were that so, we would need another explanation for the inactivation of insulin by normal blood.

Collip⁷ suggested that insulin needs a complement for its action. Lundsgaard,⁸ Brugsch⁹ and Ahlgren¹⁰ have attempted to show that a coferment is necessary for insulin to be able to affect certain steps in carbohydrate metabolism. If we attempt to apply that conception, we should have to assume that the coferment or complement is inadequate



EFFECT OF PH CHANGES OF PLASMA

- — — — — 10 c.c. PLASMA PH. 7.40
- - - - - 10 c.c. PLASMA PH. 8.0
- 10 c.c. PLASMA PH. 6.0
- . - . - 10 c.c. SALINE SOL. PH. 9.2

Chart 5.—The effect of p_H changes of plasma. The long dash line represents 10 cc. of plasma, with a p_H of 7.4; the short dash line, 10 cc. of plasma, with a p_H of 8; the continuous line, 10 cc. of plasma, with a p_H of 6, and the long dash dot line, 10 cc. of saline solution, with a p_H of 9.2.

7. Collip, J. B.: *Am. J. Physiol.* **63**:391, 1923.

8. Lundsgaard, C.; Holboll, S. A., and Gottschalk, A.: *J. Biol. Chem.* **70**: 89 (Sept.) 1926.

9. Brugsch, T., and Horsters, H.: *Med. Klin.* **22**:81 (Jan. 15) 1926.

10. Ahlgren, G.: *Klin. Wchnschr.* **3**:1158 (June) 1924; **3**:1222 (June) 1924.

in normal blood in vitro and still less in diabetic blood or that conditions were not conducive for the coferment to function.

SUMMARY

We observed the following facts:

1. The blood plasma of a diabetic child who did not respond properly to insulin inhibited the insulin action in rabbits.

2. The same phenomenon occurred with blood from normal persons, young or old.

3. A greater inhibition was caused by blood cells than by plasma.

4. A still greater inhibition occurred when the cells were laked, which showed that the inhibiting substance is found mainly endocellular, and to a lesser degree in the plasma.

5. Greater inactivation is produced by the blood from diabetic patients than that resulting from the blood of normal persons.

6. We have control experiments to show that this inactivation is not due to dilution, viscosity of the fluid, rate of absorption from under the skin or adsorption by the cells, or the p_H of the blood for the period of incubation used in our experiments, not more than two hours, except at p_H 6 or lower when the inactivation ceases and at p_H 9.2 when it is increased, most likely due to the alkali itself.

The inhibition of the action of insulin by blood depends on the quantity of the active principle. That may explain why other authors who have used blood similarly obtained negative results. They probably used less blood per unit of insulin than we did. Furthermore, the inactivation may vary with different persons and with the same person at different times, perhaps even at different hours of the day, e. g., as related to meals, exercises and the like.

CHRONIC ULCERATIVE COLITIS

A REVIEW OF INVESTIGATIONS ON ETIOLOGY *

J. ARNOLD BARGEN, M.D.

ROCHESTER, MINN.

A symposium in 1928 on chronic ulcerative colitis in the Harvein Society of London reported in the *Lancet*, in which such eminent men as French, Tidy, Norbury, Smith, Wakely, Broadbent and Wilcox took part, added nothing to knowledge of the etiology of or treatment for this disease. The participants were convinced of the infectious nature of the disease and advocated irrigations and surgical procedures in the treatment. Later the editor of *Lancet* commented¹ on the unknown etiology of the disease. Therefore, this review seems opportune.

The voluminous literature on the subject of chronic ulcerative colitis is briefly summarized as follows: Wilks and Moxon² mentioned the disease in 1875 in their lectures on pathologic anatomy. A colored drawing by Cruveilhier,³ including work reported between 1829 and 1842, presents a condition which certainly suggests chronic ulcerative colitis. Allchin, in 1885, exhibited to the London Pathological Society a specimen of a colon from a case of this disease, calling attention to features which he believed distinguished the condition as a disease entity. This was the first specimen of its kind brought before the society. White,⁴ in 1888, gave a good pathologic description of the disease. Lockhart Mummery's⁵ first description appeared in 1907 and 1908, and at this early date he emphasized the need of proctoscopic investigation, stressing the fact that knowledge before that time had been gathered chiefly from the patients' symptoms and from the postmortem examination. Allchin,⁶ in 1909, wrote about the pathology and emphasized the

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* From the Division of Medicine, the Mayo Clinic.

1. Editorial: Ulcerative Colitis, *Lancet* **2**:78, 1928

2. Wilks, Samuel, and Moxon, Walter: *Lectures on Pathological Anatomy*, ed. 2, London, J. and A. Churchill, 1875.

3. Cruveilhier, Jean: *Anatomie pathologique du corps humain ou descriptions avec figures lithographiées et coloriées, des diverses altérations morbides dont le corps humain est susceptible*, Paris, 1829-1842, vol. 2, ch. 30.

4. White, W. H.: On Simple Ulcerative Colitis and Other Rare Intestinal Ulcers, *Guy's Hosp. Rep.* **45**:131, 1888.

5. Mummery, J. P. Lockhart: The Causes of Colitis with Special Reference to Its Surgical Treatment with an Account of Thirty-Six Cases, *Lancet* **1**:1638, 1907; Chronic Colitis and Its Surgical Treatment, *Practitioner* **1**:489, 1908.

6. Allchin, W. H.: Ulcerative Colitis, *Proc. Roy. Soc. Med.* **2**:59, 1909.

unsatisfactory name of the disease. He made note of the fact that in twenty years prior to 1908, fifty-five patients with chronic ulcerative colitis had been admitted to Guy's Hospital, London. Hawkins,⁷ in 1909, expressed the belief that "the pedigree of the disease can be traced to the bloody flux of Sydenham in 1669." Cameron and Rippmann,⁸ in 1909 and 1910, reported statistics about the cases of this disease found in London hospitals from 1888 to 1910. Jex-Blake and Higgs⁹ first spoke of its bacterial etiology in 1909, considering as factors, *Bacillus coli*, *Escherichia coli*, *Bacillus proteus-vulgaris*, *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) and streptococci. Wallis,¹⁰ in 1909 reported streptococci in the stools of many of these patients and emphasized the significance of oral sepsis. White,¹¹ in 1911, noted that he "had met with cases due to *Bacillus coli* and pneumococci." Hutchison,¹² in 1911, wrote concerning the treatment of the disease, and commented on dietetic, medicinal and surgical measures. Lockhart Mummery,¹³ in 1911, reported on its diagnosis with the sigmoidoscope. Lindenberg,¹⁴ in 1912, advocated surgical treatment, describing colostomy as the procedure of choice. Wegele,¹⁵ in 1913, stressed the seriousness of rectoscopy in these cases and commented on surgical and medical treatment. Kretschmer¹⁶ also, in the same year, called attention to the exacerbations of the disease, and urged surgical procedure as a last resort. Lockhart Mummery,¹⁷ in 1913, emphasized its serious nature by reporting a fatal case. Bassler,¹⁸ in 1913, first suggested the significance of *Bacillus coli* in the condition.

7. Hawkins, H. P.: Natural History of Ulcerative Colitis and Its Bearing on Treatment, Brit. M. J. **1**:765, 1909.

8. Cameron, H. C., and Rippmann, C. H.: Statistics of Ulcerative Colitis from the London Hospitals: Guy's Hospital, Proc. Roy. Soc. Med. **2**:100, 1909; The Post-Mortem Statistics of Ulcerative Colitis at Guy's Hospital from 1888 to 1907, Guy's Hosp. Rep. **64**:353, 1910.

9. Jex-Blake, A. J., and Higgs, F. W.: Statistics of Ulcerative Colitis from the London Hospitals: St. George's Hospital, Proc. Roy. Soc. Med. **2**:119, 1909.

10. Wallis, F. C.: The Surgery of Colitis, Brit. M. J. **1**:10, 1909.

11. White, W. H.: The Principles of the Treatment of Colitis, Clin. J. **38**:49, 1911.

12. Hutchison, Robert: Treatment of Colitis, Clin. J. **38**:53, 1911.

13. Mummery, J. P. Lockhart: The Surgical Treatment of Colitis and Its Indications, Clin. J. **38**:56, 1911.

14. Lindenberg, H.: Operative Treatment of Ulcerative Colitis, abstr., J. A. M. A. **59**:1752 (Nov. 9) 1912.

15. Wegele: Ueber Colitis ulcerosa und Ihre Behandlung, Med. Klin. **9**:89, 1913.

16. Kretschmer, J.: Colitis ulcerosa, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **17**:66, 1913.

17. Mummery, J. P. Lockhart: Case of Ulcerative Colitis, Terminating Fatally, Proc. Roy. Soc. Med. **6**:209, 1913.

18. Bassler, Anthony: Ulcerative Colitis, Interstate M. J. **20**:708, 1913.

Haskell,¹⁹ in 1914, reported a case of acute ulcerative colitis. Albu,²⁰ in 1915, commented on its pathology and reported two acute and twenty-one chronic cases. Hewitt and Howard,²¹ in 1915, noted its relation to polyps of the colon. Strauss,²² in 1915, spoke of its bacterial etiology, basing his belief on the following facts: 1. In seven of his cases, there was agglutination of dysentery and typhus bacilli by these serums from human beings in dilutions of 1:50 and, in one case in dilutions of 1:150. 2. There was the occurrence of such complications as arthritis, iridocyclitis and venous thrombosis. Lynch and McFarland,²³ in 1916, first described the condition in a general consideration of "colonic infections."

Little appeared in the literature from then until the statistical study of 117 cases by Logan,²⁴ in 1919. Logan expressed the belief that the basic etiologic factor was a metabolic disturbance. Lockhart Mummery,²⁵ in 1920, advocated surgical treatment, suggesting appendicostomy as the operation best fitted to the needs of this condition. He also emphasized the predominance of streptococci and bacilli of the colon group in stools of these patients and the absence of parasites. Hurst,²⁶ in 1921, expressed the belief that the condition was a postbacillary infection. Yeomans,²⁷ in 1921, found only the usual intestinal inhabitants by cultures of stools. Leusden,²⁸ in 1921, wrote of the significance of colon bacilli and dysentery bacilli. Bassler,²⁹ in 1922, again wrote of the significance of colon bacilli, asserting that this organism became virulent under certain conditions, and ventured the designation of

19. Haskell, H. A.: *Acute Ulcerative Colitis*, Illinois M. J. **26**:595, 1914.

20. Albu, A.: *Zur Kenntnis der Colitis Ulcerosa*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:386, 1914.

21. Hewitt, J. H., and Howard, W. T.: *Chronic Ulcerative Colitis with Polyps; a Consideration of the So-Called Colitis polyposa (Virchow)*, Arch. Int. Med. **15**:714 (May) 1915.

22. Strauss, H.: *Zur Aetiologie der Dysenterie und dysenterieähnlicher Erkrankungen*, Arch. f. Verdauungskr. **21**:16, 1915.

23. Lynch, J. M., and McFarland, W. L.: *Colonic Infections: Some Rarely Observed Unclassified Types*, J. A. M. A. **67**:943 (Sept. 23) 1916.

24. Logan, A. H.: *Chronic Ulcerative Colitis: A Review of One Hundred and Seventeen Cases*, Northwest Med. **18**:1, 1919.

25. Mummery, J. P. Lockhart: *The Operative Treatment of Ulcerative Colitis*, Brit. M. J. **1**:497, 1920.

26. Hurst, A. F.: *Ulcerative Colitis*, Guy's Hosp. Rep. **71**:26, 1921.

27. Yeomans, F. C.: *Chronic Ulcerative Colitis*, J. A. M. A. **77**:2043 (Dec. 24) 1921.

28. Leusden, J. T.: *Observations on Colitis Ulcerosa with a Contribution to the Knowledge of the Pathogenic Effects of Colon Bacilli*, Nederl. Tijdschr. v. Geneesk. **65**:2890, 1921.

29. Bassler, Anthony: *Treatment of Cases of Ulcerative Colitis*, M. Rec. **101**:227, 1922.

Bacillus pseudo-dysentericus coli. Rolleston,³⁰ in 1923, wrote of the significance of primary injury to the mucosa of the colon brought on by dietary or other deficiencies and at the taking on of pathogenic characteristics by the normal intestinal inhabitants. Hewes,³¹ in 1923, wrote of the isolation of streptococci, staphylococci, colon bacilli and gas bacilli (*Clostridium welchii*) and emphasized the fact that often the disease appeared as a sequel to another infectious disease, such as pneumonia, influenza, measles or diphtheria. He stated that the infectious nature of the disease is undebatable. Stone,³² in 1923, in advocating surgical treatment, found only the usual intestinal germs. Einhorn,³³ in 1923, in commenting on treatment, considered the dysentery bacilli as significant factors early in the disease. He did not doubt the infectious nature of the disease. Brown,³⁴ in 1923, commented on the enzymatic activity of the duodenal enzymes in cases of this disease. Logan,³⁵ in 1923, reported cure of the disease in three cases in which tincture of iodine was administered by mouth. Strauss, Friedman and Bloch,³⁶ in 1924, advocated colectomy for the condition and in commenting on etiology emphasized the predominance of streptococci in washings of the colon after ileostomy. Thorlakson,³⁷ in 1923, considered bacilli of dysentery as the original invaders in the disease but called attention to the fact that diplococci resembling pneumococci had been isolated in some of his cases in pure culture. He considered these as secondary invaders. About the time of these reports, the work to be reviewed here was under way, and the following historical facts ran contemporary with my studies.

Crohn and Rosenberg,³⁸ in 1924, advocated the use of acriflavine in irrigations of the colon in the treatment of this disease, and in 1925,

30. Rolleston, Sir Humphry: Discussion on Ulcerative Colitis, Proc. Roy. Soc. Med. **16**:91, 1922-1923.

31. Hewes, H. F.: Infectious Colitis, Boston M. & S. J. **188**:994, 1923.

32. Stone, H. B.: The Surgical Treatment of Chronic Ulcerative Colitis, Ann. Surg. **77**:293, 1923.

33. Einhorn, Max: Chronic Ulcerative Colitis and Its Treatment, New York M. J. **117**:214, 1923.

34. Brown, P. W.: Duodenal Enzymes in Chronic Ulcerative Colitis, M. Clin. N. Amer. **7**:97, 1923.

35. Logan, A. H.: Three Cases of Chronic Ulcerative Colitis Cured by Iodin, M. Clin. N. Amer. **7**:105, 1923.

36. Strauss, A. A.; Friedman, J., and Bloch, L.: Colectomy for Ulcerative Colitis, S. Clin. N. Amer. **4**:667, 1924.

37. Thorlakson, P. H. T.: Primary Ulcerative Colitis, Canad. M. A. J. **14**: 1168, 1924.

38. Crohn, B. B., and Rosenberg, Herman: Medical Treatment of Chronic Ulcerative Colitis (Non-Specific), J. A. M. A. **83**:326 (Aug. 2) 1924; The Sigmoidoscopic Picture of Chronic Ulcerative Colitis (Non-Specific), Am. J. M. Sc. **170**:220, 1925.

they stressed the importance of sigmoidoscopy in the diagnosis. Rienhoff,³⁹ in 1925, advocated ileosigmoidostomy as a valuable form of treatment. In the same year, Brown⁴⁰ wrote of the protein etiology of the disease. Smith,⁴¹ in 1925, described the pathology of chronic ulcerative colitis. Rowe,⁴² in 1925, reported a case of acute ulcerative colitis, and mentioned the finding of *Bacillus coli*, pneumococci and streptococci by culture of the stools. Grossfeld,⁴³ in 1925, commented on the pathology and treatment of the condition. Lynch and Felsen,⁴⁴ in 1925, in a report of forty-one cases, expressed the belief that the colon bacillus was of etiologic significance. However, they could not ascribe this rôle to a specific bacterium, although they were firmly convinced that there was such an infectious cause. Helmholz,⁴⁵ in 1926, reported the occurrence of the disease in children. This was the first report of its kind in the literature. Carman and Moore,⁴⁶ in 1926, gave a most illuminating discussion of the roentgenologic data in this condition. Woolf,⁴⁷ in the same year, emphasized that in the thirty-five years since White's accurate description of the disease "The cause of the disease had neither been discovered, nor had much been done for the amelioration of it."

Buie,⁴⁸ in 1926 and 1928, in three reports described the proctoscopic picture so accurately that little doubt remained about the condition being an entity. Schur,⁴⁹ in 1927, expressed the belief that the condition was a definite entity of bacterial etiology. He based his belief on clinical

39. Rienhoff, W. F., Jr.: The Surgical Treatment of Chronic Ulcerative Colitis by Ileco-Sigmoidostomy, *Ann. Clin. Med.* **4**:430, 1925.

40. Brown, T. R.: Some Observations on Chronic Ulcerative Colitis, *Ann. Clin. Med.* **4**:425, 1925-1926.

41. Smith, C. E.: The Pathology of Colitis, *California & West. Med.* **23**: 1311, 1925.

42. Rowe, P. H.: Acute Ulcerative Colitis, *J. Lancet* **45**:30, 1925.

43. Grossfeld, H.: Zur Pathologie und Therapie der Colitis ulcerosa, *Arch. f. Verdauungskr.* **36**:384, 1925-1926.

44. Lynch, J. M., and Felsen, Joseph: Nonspecific Ulcerative Colitis, *Arch. Int. Med.* **35**:433 (April) 1925.

45. Helmholz, H. F.: Chronic Ulcerative Colitis in Childhood, *New York State J. Med.* **26**:46, 1926.

46. Carman, R. D., and Moore, A. B.: The Roentgenologic Findings in Ulcerative Colitis, *Am. J. Roentgenol.* **16**:17, 1926.

47. Woolf, M. S.: Chronic Ulcerative Colitis, *California & West. Med.* **24**: 191, 1926.

48. Buie, L. A.: Sigmoidoscopy in Chronic Ulcerative Colitis, *Tr. Am. Proctol. Soc.*, 1926, p. 34; Chronic Ulcerative Colitis, *J. A. M. A.* **87**:1271 (Oct. 16) 1926; Differential Diagnosis of Amebic Dysentery and Chronic Ulcerative Colitis by Proctoscopic Examination, *Surg. Gynec. Obst.* **46**:213, 1928.

49. Schur, H.: Ueber die Ursachen der Colitis Ulcerosa und Ihre Behandlung, *Wien. klin. Wchenschr.* **40**:756, 1927.

experience and a comprehensive review of the literature. Wendkos,⁵⁰ of Philadelphia, and Soper,⁵¹ of St. Louis, in 1927, reported on the use of the vaccine in the treatment of the disease and Chisholm,⁵² of Denver, reported the same in 1928. Bassler,⁵³ in 1927, stated that the condition was an infectious disease entity but that he thought it was due to a variety of bacteria, including *Bacillus coli*, diplostreptococci, *Bacillus welchii* and *Bacillus pyocyaneus*. Jones,⁵⁴ in 1927, stressed the palliative effect of surgical measures on this disease. Torrey,⁵⁵ in 1927, stressed the etiologic significance of certain streptococci and diplostreptococci in the disease. Portis,⁵⁶ in 1927, made similar observations and advocated vaccine in treatment. Alekseev,⁵⁷ of Russia, and Alessandri,⁵⁸ of Italy, in 1927, spoke of the infectious nature of chronic ulcerative colitis. Similarly, Bensaude and Oury,⁵⁹ of France, and Fenkner,⁶⁰ of Germany, in the same year, reported their belief in a bacterial etiology. Dustin,⁶¹ in 1927, in a clinical report, considered the disease to be of an infectious nature. Brown,⁶² as late as 1927, expressed the belief that "mucous," "catarrhal" and chronic ulcerative colitis were related conditions.

Crohn,⁶³ in 1929, reported that organisms of the streptococcus group were obtained by culture of the blood in two cases of severe ulcerative

50. Wendkos, S.: Chronic Ulcerative Colitis, M. J. & Rec. **125**:379, 1927.

51. Soper, H. W.: Chronic Ulcerative Colitis, Ann. Int. Med. **1**:313, 1927.

52. Chisholm, A. J.: Symptomatology and Treatment in Chronic Ulcerative Colitis, Colorado Med. **25**:28, 1928.

53. Bassler, Anthony: Ulcerative Colitis of So-Called Nonspecific Types, with Special Reference to Etiology, Pathology and Treatment, M. J. & Rec. **125**:253, 1927.

54. Jones, D. F.: The Surgical Treatment of Chronic Ulcerative Colitis, Tr. Am. Gastro-Enterol. A. **30**:172, 1927.

55. Torrey, J. C.: Symposium on Colitis: Bacteriology on the Human Colon with Particular Reference to Ulcerative Colitis, Tr. Am. Gastro-Enterol. A. **30**:129, 1927.

56. Portis, S. A.: Diagnosis and Treatment of Non-Specific Ulcerative Colitis, Illinois M. J. **51**:111, 1927.

57. Alekseev, A.: Etiology and Therapy of Chronic Ulcerative Colitis, Klin. Med. **5**:863, 1927.

58. Alessandri, Paola: La colite ulcerosa chronica; problemi attuali etiologici e terapeutici, Policlinico **34**:743, 1927.

59. Bensaude, R., and Oury, P. Quelques remarques sur les recto-colites hémorragique et purulentes et leurs traitement, J. de méd. et chir. prat. **98**:761, 1927.

60. Fenkner: Entzündliche Dickdarmerkrankungen Besonders im Gebiete des Coecum und Colon Ascendens, Arch. f. klin. Chir. **147**:682, 1927.

61. Dustin, C. C.: Chronic Ulcerative Colitis, Rhode Island M. J. **10**:147, 1927.

62. Brown, T. R.: Colitis, Catarrhal, Mucous, Ulcerative, Internat. Clin. **3**:24, 1927.

63. Crohn, B. B.: Blood Cultures in Two Cases of Chronic Ulcerative Colitis, Tr. Am. Gastro-Enterol. A., 1929.

colitis. De Bere,⁶⁴ in 1928, isolated diplostreptococci from the rectal lesions, and by intravenous injection, he produced lesions similar to those in human beings. Garrett,⁶⁵ in 1928, observed the predominance of streptococci in cultures of stools of patients with colitis. Funkhouser,⁶⁶ in the same year, made similar observations; so also did MacNaughton⁶⁷ and Santee,⁶⁸ who stressed the probable significance of specific therapy. Horgan and Horgan,⁶⁹ in July, 1929, reviewed the facts of specific treatment and reported five cases in which the results from such treatment had been good.

The only recent article with a suggestion of other than infectious etiology is a report of five cases given by Larimore,⁷⁰ in 1928, before the American Gastro-Enterological Association. The patients in the five cases had been fed on foods presumably high in vitamins in an attempt at cure. He suggested the possibility that the syndrome was the result of a food deficiency.

From this chronologic historic survey of chronic ulcerative colitis, it becomes apparent that most men who come in contact with this condition think of it in terms of infection, that they are uncertain of the bacterium or bacteria guilty of the invasion, that dysentery bacilli, or closely allied forms and various forms of streptococci have received their share of blame, and that perhaps failure to find specific bacteria may have been dependent on methods employed in trying to isolate them.

REPORT OF STUDY

Many difficulties are encountered in studying the etiology of the disease by cultures of stools. By the ordinary cultural methods, I found that bacilli of the *Escherichia coli* group and various supposed saprophytes overgrew any other forms. Injections into animals of streptococci and other bacteria isolated from plates by the usual methods gave persistently negative results. It was thought that the causative organism might be sensitive to oxygen, that perhaps a medium affording a gradient of oxygen tension might serve to enhance the growth of this organism

64. De Bere, C. J.: Ulcerative Colitis, Read before the North Side Branch of the Chicago Medical Society, March 1, 1928.

65. Garrett, F. D.: Non-Specific Chronic Ulcerative Colitis, *Southwestern Med.* **12**:50, 1928.

66. Funkhouser, A. G.: Some Phases of Ulcerative Colitis, *J. Indiana M. A.* **21**:150, 1928.

67. MacNaughton, E.: Bacteriological Studies in Chronic Ulcerative Colitis, *Canad. M. A. J.* **18**:568, 1928.

68. Santee, H. E.: Ulcerative Colitis, *Ann. Surg.* **77**:704, 1928.

69. Horgan, Edmund, and Horgan, Joseph: Chronic Ulcerative Colitis; Results of Treatment with Vaccine in Five Cases, *J. A. M. A.* **93**:263 (July) 1929.

70. Larimore, J. W.: Chronic Ulcerative Colitis; Observations of Treatment by Diet, *J. A. M. A.* **90**:841 (March 17) 1928.

in advance of other bacteria, and that the organism of which the growth had been enhanced might localize in the colon by intravenous injection of the primary culture, just as Rosenow⁷¹ has found to be the case in organisms obtained from patients with other diseases. A conveniently prepared medium which furnishes these requirements is Rosenow's dextrose brain broth.

If the results obtained were carefully checked against those obtained with ordinary mediums, such as Endo's medium, plain agar, dextrose broth and blood agar, it was thought that perhaps the causative organism or organisms might be singled out to the exclusion of other more saprophytic forms. Moreover, although the old method of stool culture might not yield the causative organisms, swabbings and scrapings from the bases of the ulcers, the surfaces of which first had been cleaned, or an attempt made actually to sterilize them, might be fruitful.

Method.—The following method was employed:

The rectum was thoroughly cleansed by repeated irrigations with warm water or solution of sodium chloride until the fluid returned clear. The patient was then placed over the Buie proctoscopic table, a sterile proctoscope or anoscope was inserted, and the surface thus exposed was thoroughly cleansed by swabbing the ulcers, or, if a particularly favorable place presented itself after the cleansing, it was swabbed with tincture of iodine. A sterile swab was then passed through the scope, and, by a twisting motion, some of the material from the base of an ulcer was drawn out and transferred immediately to warm dextrose brain broth. Or, if possible, a small Pasteur pipet was inserted instead of the swab and material was drawn out in this way. The material withdrawn was disposed of at once and in three ways: some was transferred to warm dextrose brain broth, some to warm physiologic solution of sodium chloride, and some, to glass slides for smears. The first was transferred to the incubator at once. The second was used for plating purposes, in shake cultures both of blood agar and of plain agar, and for streak plates of Endo's medium. Dilutions varied with specimens obtained, but it was soon learned that considerable dilution was necessary if one wanted individual colonies separated far enough so that they could be picked from twelve to eighteen hours later with a fine platinum wire. Smears of the third specimen, stained by Gram's method and carbol fuchsin, were examined for acid-fast bacilli and for the predominating bacteria. Stools previously had been examined for *Endamebas* and other parasites.

Diligent search for bacilli of dysentery was instituted, but without success. However, large numbers of gram-positive diplococci were found in smears from the lesions in the bowels of patients with chronic ulcerative colitis. The diplococci frequently were so numerous, particularly in smears of the more acute, more severe cases, that other bacteria were not seen.

The organisms also were found in predominating numbers in primary cultures in dextrose brain broth, the medium used by Rosenow and

71. Rosenow, E. C.: Studies on Elective Localization: Focal Infection with Special Reference to Oral Sepsis, *J. Dent. Res.* 1:205, 1919.

others in studies on localization. It was believed, therefore, that growth of the causative organism might occur in this medium, since it afforded a gradient of oxygen tension, whereas only the more saprophytic organisms, or those not sensitive to oxygen, might develop on blood agar and in other ordinary mediums. Furthermore, localization in the colon might occur following intravenous injection of the primary mixed culture, and the causative organism might be isolated from the tissues of animals in which lesions developed. Thus, the animal would be used virtually as an artificial culture medium for selection of the organism that could do specific harm. Moreover, if pure cultures of the organism injected similarly after rapid subculture would produce similar lesions, such an organism could justly be considered as being a probable factor in the production of chronic ulcerative colitis. Positive results were established early in these investigations.

Healthy rabbits, weighing about 2 Kg., and free from diarrhea, as noted by several days' observation, were chosen. They were given greens, oats, hay and water, and were observed daily. Two or more rabbits received intravenous injection of cultures from each patient. In the earlier work from 2 to 5 cc. of a twenty-four hour dextrose brain broth culture, containing the diplococcus in predominance, was injected. Later from 3 to 12 cc. of a pure, rapidly isolated culture of the diplococcus was similarly injected. Rabbits that survived the inoculation were chloroformed for examination in from one to twenty-eight days, depending on the symptoms. Whether the rabbit died naturally or was chloroformed, at necropsy cultures were made from the blood, abdominal lymph nodes, spleen, and, in a few instances, from the lesions in the colon. Tissues were preserved in neutral formaldehyde for future examination or in Kaiserling's solution for museum purposes.

In smears from the lesions of patients, two organisms were seen: a gram-positive diplococcus and a gram-negative bacillus. In dextrose brain broth cultures made from the majority of the patients, the gram-positive diplococcus grew in predominance. On Endo's medium, a gram-negative bacillus grew, which in all essentials was like a colon bacillus. It was learned that at times, if tubes were heated slightly, gram-negative bacilli could be materially reduced in numbers, and often their growth could be inhibited completely.

The diplococcus did not grow on primary isolation on the surface of solid mediums, including blood agar, but after repeated subculture it grew characteristically as a fine colony on the surface. Furthermore, in shake culture it often appeared earlier in the depths of the medium.

As time went on, the technic adopted for cultivating material, obtained with sterile cotton swabs through the proctoscope from the bases of ulcers, was as follows:

Two cotton swabs that had been pressed against the bases of ulcers and rotated were placed immediately, one each in two tubes of dextrose brain broth, and were

incubated for from four to six hours. After from four to six hours, one set of three additional tubes of dextrose brain broth was inoculated with material from one of the original two tubes by simply shaking the swab into each of the three tubes of sterile dextrose brain broth. A second set of three tubes was similarly inoculated with material from the other of the original two tubes. One set of three tubes was heated for forty-five minutes at 55 C. and incubated; the other set of three tubes was incubated directly without heating. In eighteen hours, smears were made of the growth in each of the eight tubes of dextrose brain broth, the smears were stained by Gram's method, with safranin as a counterstain, and examined with the purpose of selecting the tube with the largest predominance of diplococci of the variety that is to be described. Subcultures of this were made on blood-agar plates. Cultures on Endo's medium and in dextrose broth had been made from the original swabs and were now examined. The growth here was predominantly, and usually, wholly of gram-negative bacilli, which by further study were found to belong to the *Escherichia coli* group.

The subculture for the first blood-agar plate was made by mixing one drop of inoculated dextrose brain broth from a capillary tube, with 10 cc. of physiologic solution of sodium chloride and one drop of this mixture, from a capillary tube, in 10 cc. of blood agar. Several dilutions were made from the subculture. These plates were incubated overnight.

The following morning colonies of diplococci were surrounded by a green zone, with a faintly hemolytic zone between the colony and the green zone. The colonies were picked with a platinum wire, were transferred to fresh tubes of dextrose brain broth and were incubated for eighteen hours. Smears of these were stained. The diplococci usually were rather closely fused in pairs, almost merging into a chain of four cocci. The organism so isolated has the following characteristics: It is lancet-shaped, slightly larger than a pneumococcus, gram-positive, and from early subculture, never appears in smears as more than two or four diplococci in a group. The appearance of its colony on blood agar is typical; so also is that on mannite agar, where it appears as a fine translucent colony, in striking contrast to the so-called enterococcus of Houston and McCloy,⁷² which grows as a large white opalescent colony on this medium. The colony of *Streptococcus fecalis* appears much like that of the enterococcus. The diplococcus and enterococcus do not usually ferment mannite; *Streptococcus fecalis* does. The diplococcus does not ferment inulin; the *Diplococcus pneumoniae* does. The diplococcus ferments dextrose, lactose, saccharose, maltose, raffinose and salicin.

With full realization of the uncertain status of the so-called enterococcus in modern bacteriologic classifications, I am referring, when using this term, to the organism described by Houston and McCloy, isolated by culture of stools from soldiers suffering from trench fever.

72. Houston, Thomas, and McCloy, J. M.: The Relation of the Enterococcus to "Trench Fever" and Allied Conditions, *Lancet* 2:633, 1916.

He described an organism similar to or identical with *Micrococcus ovalis* of Escherich.⁷³ He isolated it by culture of stools in a great variety of conditions found during the war. He expressed the belief that it is "a constant inhabitant of the normal bowel. It differs from all other streptococci by the ease with which it grows on ordinary laboratory media and by its greater power of resistance; that is, cultures of it survive longer and are more difficult to kill. It grows well on all ordinary laboratory mediums under both aerobic and anaerobic conditions. On agar it forms a fine growth not unlike that of *Streptococcus pyogenes*, but the individual colonies are larger and more opaque. On gelatin at room temperature it forms a white growth in twenty-four hours and does not liquefy the medium. On Conradi-Drigalski's medium it grows well; in twenty-four hours the size of the individual colonies is intermediate between that of *Bacillus coli* and an ordinary streptococcus, and the medium becomes red. In broth the enterococcus grows well, producing a uniform turbidity and forming comparatively short chains and diplococci. It rapidly ferments dextrose, lactose, and saccharose, more slowly salicin; no change in mannite could be demonstrated in one week. Its resistance to heat is remarkable. A thick emulsion of the coccus in broth or physiologic solution of sodium chloride contained in a test tube was found in numerous experiments to be alive after an exposure for one and a half hours to a temperature of 55 C.

Other significant differences between the so-called enterococcus and the diplococcus of chronic ulcerative colitis are these: The diplococcus does not grow on plain agar, or only after repeated subculture and then sparingly; it does not grow on gelatin, and it does not coagulate milk.

To classify the organism of chronic ulcerative colitis one must take into consideration its tendency to form chains, after repeated subculture, its lack of power to ferment inulin, its green zone on blood agar, and its tendency to localize in tissues after intravenous inoculation, like other streptococci. It probably belongs to the streptococcus group, and the viridans species.

With this organism, rabbits have been immunized to produce a diagnostic serum. The diplococcus was grown in 100 cc. of 0.2 per cent dextrose broth for twenty-four hours. The broth culture was centrifugated, the supernatant fluid was decanted, and the precipitate was suspended in 100 cc. of physiologic solution of sodium chloride. This was preserved at the temperature of the icebox. Five tenths of a cubic centimeter of this suspension in solution of sodium chloride, was injected intravenously into a large rabbit; every two days another injection was made, and the amount was increased 0.5 cc. each time.

73. Escherich, T.: Die Darmbakterien des Neugeborenen und des Säuglings, Fortschr. d. Med. 3:515 and 547. 1885.

When agglutination took place in dilutions well up between 1:1,000 and 1:10,000, which may occur in several weeks as determined by successive bleeding and titration of the serum, the intervals between injections were lengthened to once a week or once in ten days, which was sufficient to maintain the titer. As the work progressed, the other criterion by which identity of the diplococcus was established was determination of agglutinins and precipitins in the serums of these rabbits. The agglutination of the diplococcus in suspension in physiologic solution of sodium chloride usually occurred in a dilution well above 1:1,000 and many times as high as 1:10,000.

Horses also were immunized by the methods of Rosenow,⁷¹ and precipitins and agglutinins were determined with their serums.

In many of the rabbits given intravenous injections with the larger doses of the primary culture in dextrose brain broth, in which diplococci were the vastly predominating bacteria, or with the pure cultures made by rapid subculture of the original culture, severe diarrhea developed in from twenty-four hours to several days after the injections. Often there was blood and mucus in the stools. The rabbits lost weight and wasted rapidly.

In 189 cases (approximately 80 per cent) of chronic ulcerative colitis in which the patients were examined at the Mayo Clinic over a period of several years, the diplococcus was isolated in pure culture. With these strains, 459 healthy rabbits were given injections. Evidence of disease of the large intestine, from marked diarrhea with few, if any, hemorrhages, to extensive hemorrhages and severe ulceration with bloody discharges from the rectum, developed in 268 rabbits. The seat of election of these lesions corresponded rather accurately to that in the patients. Lesions, as a rule, were more extensive near the rectum and often involved only the distal half of the colon.

In a few instances, lesions occurred in other parts of the gastrointestinal tract in the form of submucous and disseminated hemorrhages. Rarely were lesions found in any other organs of the body.

Similar cultures were made in ninety-eight consecutive control cases in which proctoscopic examinations were made and in which the mucosa of the bowel was normal. Diplococci, in some essentials like those found in cases of chronic ulcerative colitis, were isolated from sixteen cases. Six of these strains were agglutinated by the immune horse serum used diagnostically and therapeutically; only four produced lesions in animals. These lesions were in the form of a few minute, disseminated hemorrhages in the colon. Other strains of streptococci were frequently isolated. None produced lesions in rabbits similar to those described.

Rosenow, Nickel, Meisser, Hufford, Cook and others, working along similar lines, with similar cultural methods in conditions other than

chronic ulcerative colitis, with other strains of streptococci, in the same laboratory, during the same period, with animals from the same common stock, induced lesions in the colon only in rare instances (not more than 2 per cent).

In twenty-one of twenty-five dogs which were given injections in a manner similar to that used in rabbits with from 3 to 15 cc. of a dextrose brain broth culture of the diplococcus, even more striking and more characteristic lesions of the colon occurred. In several dogs, bloody diarrhea was so severe that rectal prolapse occurred, providing ample opportunity to observe with the naked eye lesions like those seen with the proctoscope in human beings. Several other dogs were examined proctoscopically and the typical lesions observed.

An organism, in all essentials like the diplococcus described was isolated by blood culture from six patients with severe fulminating, acute ulcerative colitis. All these patients were acutely ill with a high septic type of fever, marked abdominal tenderness and extensive involvement of the colon. Three of the six patients died, and in two the organism was isolated at necropsy from the heart's blood. In sections through the lesions in the colon in these cases, and in sections through the ulcers in the colons of twelve other patients who died from chronic ulcerative colitis, large numbers of diplococci morphologically like those described were demonstrated in the depths of the inflammatory and granulation tissue. The Gram-Weigert method of staining of tissues for bacteria was used.

Another seemingly significant factor bearing on the causative relation of bacteria to this disease is the clinical observation that frequently tonsillectomy, removal of infected teeth or acute infections of the upper respiratory tract, cause marked acute temporary exacerbations of the disease. This suggests the presence of the causative bacteria in these foci.

Diplostreptococci, in all essentials like those isolated from the rectal lesions, have been isolated from periapical abscesses of teeth or from buried tonsillar abscesses, and cultures of these when injected intravenously have produced in animals lesions like those described. These organisms were agglutinated by the immune rabbit and horse serums. This has been the experience with the use of strains from many patients on several hundred rabbits.

Cook, working with Rosenow, has induced periapical infections at the apexes of teeth of a series of dogs by removing the pulp and inoculating the pulp canals with dense suspensions of diplococci isolated from the blood and mesenteric lymph nodes of rabbits in which hemorrhagic colitis developed following intravenous injection of diplococci which in turn had been isolated from the lesions or foci of patients with chronic ulcerative colitis. From eight to twelve months later, chronic

ulcerative colitis developed in a number of these dogs and was demonstrated proctoscopically and at necropsy.

Complications of chronic ulcerative colitis are multiple, and perirectal abscess is one of the more serious of them. On several occasions in localized perirectal abscesses which have occurred in the course of this disease, pure cultures of a diplostreptococcus have been isolated at the time of first drainage of the abscesses.

Finally, on the basis of the belief that these observations seem to establish this diplostreptococcus as significant in the etiology of chronic ulcerative colitis autogenous vaccines have been prepared and used as part of the treatment in the more chronic cases. Moreover, horses immunized by Rosenow with this organism have produced a serum of good titer, and this serum is being used in the treatment of patients with the more severe, acute cases. The results with these forms of treatment have given far better results than any form of treatment hitherto suggested. Approximately 70 per cent of patients have returned to normal, useful lives.

CONCLUSIONS

Chronic ulcerative colitis is an infectious disease involving primarily the colon. It has characteristic clinical, proctoscopic, pathologic and roentgenologic features.

A diplostreptococcus isolated from the lesions in the rectum, in distant foci, in the blood of the patients with the more acute stages of the disease, during life and after death, and demonstrated in the lesions in fatal cases has etiologic significance in chronic ulcerative colitis.

THE VALUE OF THE INDICAN DETERMINATION IN THE BLOOD IN CASES OF RENAL INSUFFICIENCY*

B. L. MONIAS, PH.D.

AND

P. SHAPIRO, M.D.

CHICAGO

The early recognition of functional impairment of the kidney, which will sooner or later terminate in uremia, is one of the most important problems in the diagnosis and treatment of the various forms of renal disease. Recent progress in chemical analysis of the blood has been great, particularly with regard to the accumulation of nitrogen waste products as a sign of renal insufficiency. Yet often one will be disappointed in diagnosis and prognosis if too much stress is laid on the nonprotein nitrogen, the urea nitrogen, the uric acid or the creatinine readings of the blood.

For one may find excessive amounts of these substances in patients who die of myocardial insufficiency, and in whom, apart from passive congestion, the kidneys show no anatomic changes. If such patients recover, improvement of the function of the heart also quickly ameliorates the chemical condition of the blood. In cases of pneumonia or other infections or in cachectic states of varied cause one may be similarly misled. On the other hand, considerable renal parenchyma can be destroyed without markedly affecting the urea, the uric acid or the creatinine content of the blood. Accumulation of nitrogen waste products may appear very late and to limited degree, yet the patient soon dies of uremia.

In addition to the nitrogenous substances mentioned, indican has repeatedly been suggested as a sensitive indicator of renal insufficiency. This indicator is said to have the advantage of detecting the seriousness of the conditions at a time when the other substances of the blood are still within normal limits. The appearance of indican seems to be dependent only on the functional state of the renal parenchyma, and is little if at all influenced by mere congestion of the kidney or by non-renal conditions. Its appearance is conclusive evidence of an impending and fatal insufficiency of the kidneys, that is, of uremia.

Indican is derived from indole, which is formed by putrefaction in the intestine from aromatic radicals of the proteins. Indole is absorbed

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* From the Uihlein Memorial Laboratory of the Grant Hospital and the Department of Pathology of the Cook County Hospital.

from the intestinal tract, and in passing through the body is oxidized to indoxyl. In the liver, indoxyl unites with sulphuric and glycuronic acid. Indican is the potassium salt of the indoxyl-sulphuric acid. With normal kidneys, it is promptly excreted by them even if excessive amounts of indole are formed in the intestine. With the earliest absolute impairment of the renal parenchyma, the kidneys become unable to excrete the amount of indican normally formed. Its excretion is stopped even when urea nitrogen and creatinine are still passed through. It ceases to appear in the urine and accumulates in the blood.

Obermeyer and Popper, in 1911, were the first to demonstrate the indicanemia of uremia. They used the same method which is applied to the urine (ferric chloride-hydrochloric acid test). Jolles modified this method, making it much more sensitive, so that the determination of indican in the blood was placed on a quantitative basis as accurate as the creatinine or urea nitrogen readings. With the Jolles modification, the indoxyl is transformed into indigolignon, which because of its intense violet coloration can be detected in the faintest traces. With the aid of this highly sensitive test, Haas was able to detect traces of indican even in the blood of normal persons. Values of 0.2 mg. per hundred cubic centimeters of blood, or more, are abnormal and indicate a renal insufficiency. Baar found that in cases of uremia the indican may rise to 3 and even to 10 mg. per hundred cubic centimeters. The great value of the determination of blood indican in renal disorders was confirmed by several investigators, notably Umber and Rosenberg, Schilling, Eufinger, Mute, Baar and Krokiewicz.

Thus far, no work on indicanemia has been done in this country or in Great Britain. It is our purpose in this paper to call attention to this method, which, in our hands, has proved satisfactory.

DETERMINATION OF INDICAN IN THE BLOOD

Either oxalated plasma or serum may be used. Plasma has the advantage that one need not wait for the clot to separate from the serum, and in that it can be taken from the samples already collected for the determination of the nonprotein nitrogen, urea nitrogen and creatinine. However, it is essential to use lithium oxalate, since potassium oxalate seems to interfere with the color reaction (as it does also in the determination of uric acid). Serum has the advantage that no special lithium oxalate bottles are required. The blood sample may be placed in any available tube.

The following reagents are required: (1) 20 per cent trichloroacetic acid; (2) 5 per cent alcoholic solution of thymol; (3) concentrated fuming hydrochloric acid (clinically pure, specific gravity, 1.19), containing 0.5 per cent ferric chloride; (4) chloroform (Merck's reagent, chemically pure), and (5) distilled water.

The following apparatus is required: (1) a 100 cc. graduated cylinder, preferably with glass stopper; (2) an Erlenmeyer flask, of about a 200 cc. capacity, and (3) a filter funnel.

Quantities may be measured either gravimetrically or volumetrically. Five grams or cubic centimeters of the separated plasma or serum is placed in an Erlenmeyer flask. An equal amount of distilled water is added. The mixture is precipitated by adding an equal quantity, i.e., 10 Gm. or cc., of the trichloroacetic acid. The flask is then rotated for about two minutes. After five minutes the contents are filtered into the graduated cylinder. Through a capillary pipet, 10 drops of the thymol solution are added to the clear filtrate. Then is added an amount of the hydrochloric acid-ferric chloride solution equal to that of the filtrate obtained. The mixture is shaken well and allowed to stand for two hours. Then 5 cc. of chloroform is added, and the mixture is shaken for two or three minutes and allowed to stand. The chloroform dissolves out the indigo and promptly settles to the bottom.

For accurate, quantitative readings, the chloroform is pipetted off, and the intensity of its coloration is compared with an artificial or natural standard solution. A Dubosque or Autenrieth colorimeter is used for this purpose.

Preparation of the Natural Standard.—Three milligrams of indican is dissolved in 30 cc. of chloroform, and placed in a graduated glass cylinder. To this solution is added 30 cc. of a 0.5 per cent solution of ferric chloride in concentrated hydrochloric acid, and 30 capillary drops of a 5 per cent alcoholic thymol solution. The mixture is shaken well and left standing for two hours. The colored chloroform is pipetted off, and the remaining solution is shaken with another 10 cc. of chloroform which is added to the portion previously removed. This procedure is repeated until the total amount of chloroform is 60 cc. This 60 cc. contains 3 mg. of indican; 10 cc. contains 0.5 mg., or 100 cc. contains 5 mg. By using this chloroform solution as the standard, the calculation of the unknown quantity is done as follows:

$$\frac{\text{Reading of the standard} \times 0.5}{\text{Reading of the unknown} \times 10} = \text{milligrams of indican per hundred cubic centimeters of blood.}$$

If the coloration of the standard is too intensive, further dilutions may be made with chloroform. Of course, these dilutions are taken into consideration in calculating the unknown quantity.

Preparation of the Artificial Standard.—Indican cannot be obtained on the market. It is cumbersome to prepare and requires special technical skill and laboratory facilities. Prof. Dr. F. Silberstein of the Institute of Experimental Pathology of the University of Vienna supplied us with a quantity of indican sufficient to prepare a natural standard. The necessity of preparing an artificial standard has been recognized by earlier investigators. Thus, Erick suggested a mixture of scarlet red and eriglaucin (Gruebler). For our artificial standard, we selected two dyes which are found in every laboratory, namely, eosin (water soluble, yellow) and gentian violet. The artificial standard consists of 6 capillary drops of a 1 per cent solution of gentian violet in water, 3 drops of a 1 per cent solution of eosin in water, 10 cc. of 94 per cent alcohol and 30 cc. of distilled water. This mixture corresponds in tint and intensity to the original standard of 5 mg. of indican in 100 cc. of chloroform. From the stock solution, various dilutions may be made, water being used as a diluent. Besides being easily obtainable, this artificial standard has the advantage of not fading. The higher dilutions of the natural standard fade with time.

To facilitate the dilutions of the standards, the accompanying tables are given.

Simplification of the Method for Use by the Practitioner.—The use of either of these standards firmly establishes the determination of indicanemia as a quanti-

tative laboratory method that is as accurate as the urea nitrogen or creatinine readings. But laboratory facilities are not always available in the stress of practice. Diagnosis and prognosis often cannot wait on a report of the chemistry. Further, the expense of any determination of blood chemistry may be a burden to the patient. We have therefore attempted to simplify the determination of indicanemia so that it may be performed by the practitioner in his own office with a minimum of time and effort and with an accuracy sufficient for his immediate needs.

For this purpose, the test is given just as described. Volumetric quantities are usually easier to follow. No standards or colorimeter are required. When the chloroform settles to the bottom of the graduated cylinder in which it has been

TABLE 1.—(Standard 1) *Dilutions of Standard Solutions with Equivalents of Indican*

Amounts of Stock Solution, Cc.*	Amount of Chloroform Added, Cc.	Equivalent of Indican, Mg.†	Index of Intensity of Indican
10	0	0.5	
9	1	0.45	4+
8	2	0.40	
7	3	0.35	
6	4	0.30	3+
5	5	0.25	
4	6	0.20	
3	7	0.15	2+
2	8	0.10	

* Stock solutions of smaller amounts may be used.

† One hundred cubic centimeters of the stock solution corresponds to 5 mg. of indican.

TABLE 2.—(Standard 2) *Dilutions of Standard Solutions with Equivalents of Indican*

Amount of Stock Solution, Cc.*	Amount of Chloroform Added, Cc.	Equivalent of Indican, Mg.†	Index of Intensity of Indican
10	0	0.05	
9	1	0.045	1+
8	2	0.040	
7	3	0.035	
6	4	0.030	Trace
5	5	0.025	
4	6	0.020	
3	7	0.015	
2	8	0.010	Negative
1	9	0.005	

* Stock solutions of smaller amounts may be used. Solutions may be prepared from the artificial stock standard (10 cc. or 0.5 mg. of indican) in the same way as the natural standard solutions, water being used as a diluent.

† One hundred cubic centimeters of the stock solution corresponds to 0.5 mg. of indican.

shaken, it is directly observed. If it is a deep blue, marked indicanemia is present and the patient will die in uremia. If it is colorless or only faintly blue, there is no significant indicanemia and consequently no uremia. Intermediate or doubtful color reactions are not often encountered. When they occur, they have the same significance as an intermediate elevation of urea nitrogen: i. e., the patient bears watching. A practical makeshift standard may be found in the ordinary Dunning colorimeter used for tests of phenolsulphonphthalein excretion. A color corresponding to 40 or above on the Dunning colorimeter is the indication of a grave indicanemia; one below 15 shows a negligible degree. The entire test requires about ten minutes and but a few simple pieces of apparatus. In two hours the determination is available for reading and for clinical use.

TABLE 3.—*Marked Indicanemia, Showing High Urea Nitrogen Values; Death in Uremia*

No.; Pa- tient	Race, Sex and Age	Clinical Diag- nosis	Blood Chemistry				Cause of Death	Date, 1929	Postmortem Data When Autopsy Was Permitted
			Date, 1929	Urea Nitrogen, Mg. per 100 Cc. of Blood	Oreat- inine	Indi- can +			
1 V. F.	Colored Male 52	Chronic diffuse nephritis	3/20	139.6	13.3	4	Uremia	3/24	Chronic glomerulonephritis, the extracapillary form
2 L. R.	Colored Female 33	Chronic diffuse nephritis	3/16	144.7	8.0	4	Uremia	3/12	
3 J. C.	White Male 48	Chronic diffuse nephritis	3/13/	132.6	9.2	4	Uremia	3/14	
4 I. W.	Colored Female 50	Chronic diffuse nephritis	3/18	173.0	12.0	4	Uremia	3/21	(P.M. 250) Primary contracted kidney; malignant renal arteriosclerosis; uremic colitis
5 H. E.	White Male 32	Chronic diffuse nephritis	5/ 2	108.0	9.3	4	Uremia	5/ 6	
6 R. T.	Colored Male 36	Chronic diffuse nephritis	5/28	172.0	15.5	4	Uremia	3/29	(P.M. 450) Chronic glomerulonephritis
7 N. R.	Colored Male 32	Chronic diffuse nephritis	4/16	100.0	10.0	4	Uremia	4/22	(P.M. 340) Primary contracted kidney; malignant renal arteriosclerosis; uremic colitis
8 O. H.	Colored Male 39	Chronic diffuse nephritis	4/16	102.7	12.0	4	Uremia	4/18	
9 P. H.	Colored Male 59	Chronic diffuse nephritis	5/ 6	107.2	6.7	4	Uremia	5/ 9	(P.M. 394) Primary contracted kidney; malignant renal arterio sclerosis
10 T. N.	Colored Male 24	Chronic diffuse nephritis	6/15	120.0	13.0	4	Uremia	6/17	
11 P. B.	White Female 45	Chronic diffuse nephritis	6/24	120.0	9.2	4	Uremia	6/28	
12 L. N.	White Female 32	Chronic diffuse nephritis	3/ 4 3/18	72.0 145.7	6.5 10.9	4 4	Uremia Uremia	3/13	
13 J. B.	Colored Male 47	Chronic diffuse nephritis	4/25 5/ 6	103.0 170.0	11.0 12.0	4 4	Uremia Uremia	5/ 7	
14 C. D.	Colored Male 20	Chronic diffuse nephritis	5/ 4	84.0	13.3	4	Uremia	5/ 7	
15 S. B.	White Male 27	Subchronic diffuse nephritis	6/15	124.0	8.3	4	Uremia	6/17	
16 L. P.	Colored Female 44	Primary contracted kidney	3/30	107.0	9.3	4	Uremia	4/ 3	
17 L. D.	Colored Male 30	Chronic pyelo- nephritis	5/ 3	84.0	10.0	4	Uremia	5/ 4	(P.M. 462) Chronic pyelo-nephritis with marked reduction of the renal parenchyma
18 T. W.	White male 78	Pyelo- nephritis	6/20	80.0	8.0	4	Uremia	6/24	
19 W. B.	Colored Male 54	Urinary retention from a gonorrheal ureteral stricture	3/27	78.0	7.0	4	Uremia	3/30	
20 G. B.	White Male 67	Hyper- trophied prostate	5/ 6	73.0	5.0	3	Uremia	5/10	

OBSERVATIONS

To establish the reliability and clinical value of this chemical analysis of the blood for indican, 104 cases were picked at random. The observations on indican and their implication with respect to renal insufficiency were compared with those of the urea nitrogen and creatinine readings. Special stress was laid not only on the clinical diagnosis, but on the ultimate fate of the patients and, if permission could be

TABLE 3.—*Marked Indicanemia, Showing High Urea Nitrogen Values; Death in Uremia—Continued*

No.; Pa- tient	Race, Sex and Age	Clinical Diag- nosis	Blood Chemistry				Cause of Death	Date, 1929	Postmortem Data When Autopsy Was Permitted
			Date, 1929	Urea Nitrogen Mg. per 100 Cc. of Blood	Creat- inine	Indi- can +			
21 B. B.	Colored Female 52	Primary contracted kidney	4/16	64.0	8.0	4	Uremia	4/27	
22 C. B.	White Male 25	Chronic diffuse nephritis	4/17	51.0	6.0	4	Uremia	4/18	(P.M. 323) Chronic glomerulonephritis; uremic colitis
23 M. M.	White Male 23	Chronic diffuse nephritis	3/11	38.8	2.6	4	Uremia	3/26	
24 R. N.	White Male 45	Chronic diffuse nephritis	3/13	56.0	4.6	4	Uremia	3.20	
25 L. L.	White Female 15	Chronic diffuse nephritis	4/20	45.0	3.0	3	Uremia	5/ 7	
26 M. C.	Colored Female 48	Chronic diffuse nephritis	4/ 7 5/ 1 5/ 7 5/ 8	50.0 70.0 50.0 44.0	3.0 7.5 3.0 2.8	4 4 4 4	Uremia	5/ 8	
27 M. S.	Colored Female 38	Chronic diffuse nephritis	4/20	42.0	3.0	4	Uremia	5/20	
28 A. J.	Colored Male 33	Chronic diffuse nephritis	4/11	47.0	3.5	4	Uremia	5/25	
29 C. H.	White Male 27	Tubercu- lous pyelo- nephritis	3/13	48.0	3.3	4	Uremia	4/28	
30 F. B.	White Male 60	General- ized tuber- culosis	4/16	60.0	4.3	4	Uremia	4/18	(P.M. 336) Primary con- tracted kidney; malig- nant renal arteriosclero- sis; tuberculous peri- tonitis
31 D. C.	White Male 50	Primary contracted kidney	3/20	53.0	6.6	4	Uremia	4/ 1	

obtained, on observations at autopsy. The cases were divided into four groups, according to the amount of indican in the blood.

Group 1 comprises the cases with the most intensive indicanemia, showing a range of indican from 2.5 to 5.0 mg. per hundred cubic centimeters of blood. (Excessive values of 10 mg. and over, as described by other investigators, were not encountered by us.) The degree of retention is expressed in + signs; + 3 means from 2.5 to

TABLE 4.—*Absent or Faint Indicanemia, with Low or Moderate Urea Nitrogen Values; Death from Other Causes than Uremia*

No.; Pa- tient	Race, Sex and Age	Clinical Diagnosis	Date, 1929	Blood Chemistry			Cause of Death	Postmortem Data
				Urea Nitrogen, Mg. per 100 Cc. of Blood	Cre- at- inine	Can		
32 M. B.	Colored Female 36	Hyperten- sive disease of the heart	4/ 3	34.0	2.2	0	Cardiac decompen- sation	
33 J. B.	White Male 76	Hyperten- sive disease of the heart	2/26	26.0	2.0	0	Cardiac decompen- sation	
34 S. M.	White Male 46	Hyperten- sive disease of the heart	2/27	18.7	...	+	Cardiac decompen- sation	
35 A. M.	White Female 71	Hyperten- sive disease of the heart	4/27	40.0	2.3	+	Cardiac decompen- sation	
36 C. W.	Colored Female 33	Chronic diffuse nephritis	4/15	28.0	2.0	+	Cardiac decompen- sation	
37 N. H.	White Female 90	Chronic diffuse nephritis	4/ 2	28.0	2.0	0	Cardiac decompen- sation	
38 C. M.	Colored Male 49	Syphilitic disease of the heart	3/18	30.0	2.0	0	Peritonitis	(P.M. 247) Diffuse periton- itis following perforated empyema of the appendix
39 J. H.	Colored Male 56	Hyperten- sive disease of the heart	2/25	32.0	3.0	+	Hemorrhage from bleeding peptic ulcer	
40 C. J.	White Male 53	Hyperten- sive disease of the heart	4/16	23.0	1.9	+	Hemorrhage from bleeding peptic ulcer	(P.M. 349) Chronic gastric ulcer with exposed and opened artery in its base
31 A. W.	Colored Female 48	Hyperten- sive disease of the heart	3/29	23.6	2.3	+	Pneumonia	
42 L. D.	White Male 65	Hyper- trophied prostate	3/12	43.0	3.0	0	Cardiac decompen- sation	
43 J. W.	Colored Male 35	Severe burns with hematuria	3/ 1	12.0	...	0	Burn shock	
44 W. W.	Colored Male 38	Syphilitic disease of the heart	3/19	25.7	1.8	0	Pneumonia	
45 P. H.	White Female 71	Uremia	5/24	15.0	1.4	0	Cerebral thrombosis	(P.M. 442) Cerebral hem- orrhage
46 J. K.	White Female 36	Chronic diffuse nephritis	3/10	17.0	1.7	+	Pneumonia	
47 G. M.	Colored Male 51	Pulmonary tubereu- losis	2/25	41.0	...	0	Pulmonary tuberculosis	(P.M. 470) Fibrocaceous, acino-nodose tuberculosis of the lungs
48 B. P.	White Female 12	Septic menin- gitis	4/ 4	41.0	2.1	0	Septic meningitis	
49 A. A.	White Male 55	Carcinoma of the gall- bladder	4/ 3	44.0	2.3	0	Cachexia	
50 W. K.	White Male 49	Scurvy	2/28	45.0	2.6	0	Scurvy	

3.5 mg. per hundred cubic centimeters of blood and ± 4 means from 3.6 to 5 mg. These cases would present a deep purple color in the test for indican, and the value would correspond to 40 or above on the Dunning

TABLE 5.—*Absent or Faint Indicanemia, with Marked Increase of Urea Nitrogen; Death from Causes Other Than Uremia*

No.: Pa- tient	Race, Sex and Age	Clinical Diagnosis	Date, 1929	Blood Chemistry			Cause of Death	Postmortem Data
				Urea Nitrogen, Mg. per 100 Cc. Cre- Blood	at- inine	Indi- can		
51 J. M.	White Male 54	Hyperten- sive disease of the heart	6/28	45.0	3.8	+	Cardiac decompen- sation	(P.M. 496) Eccentric hyper- trophy of the heart; chronic passive congestion
52 F. F.	White Female 35	Uremia	6/22	45.0	3.2	0	Pneumonia	
53 N. T.	White Female 75	Chronic myocar- ditis	2/25	70.0	...	+	Cardiac decompen- sation	P.M. A case for the cor- oner; chronic myocarditis; no renal damage
54 R. L.	White Male 64	Hyper- trophied prostate	4/ 1 4/ 3	28.5 59.0	3.3 ...	0 0	Postoperative broneho- pneumonia	
55 R. A.	White Male 65	Hyper- trophied prostate	3/16 3/19 3/25	75.0 60.0 53.0	5.0 3.7 3.4	++ ++ ++	Postoperative cardiac decompensation	
56 W. J.	White Male 70	Carcinoma of prostate	2/ 8	52.0	3.0	0	Pneumonia	
57 J. M.	White Female 40	Primary anemia	6/24	82.0	4.8	+	Primary anemia	(P.M. .95) postpurperal sepsis and secondary anemia
58 K. H.	White Male 55	Stone in the bladder	3/ 4	73.0	5.0	+	Postoperative cardiac de- compensation	
59 H. C.	White Male 54	Urinary retention	2/26	50.0	...	+	Cardiac decompen- sation	
60 J. P.	White Male 47	Exoph- thalmic goiter	2/ 9 2/25	20.0 71.0	...	0 +	Thyroid crisis	
61 V. B.	White Male 59	Carcinoma of the gall- bladder	3/ 5	64.4	...	+	Cachexia	(P.M. 204) Carcinoma of the gallbladder
62 F. H.	White Male 61	Pneumonia	3/12	49.0	3.3	0	Pneumonia	
63 G. D.	White Male 45	Uremia	6/ 8	51.0	3.0	0	Pneumonia	(P.M. 476) Bronchopneu- monia
64 G. L.	Colored Male 53	Hyperten- sive disease of the heart	5/20 6/24	9.3 72.0	...	0 +	Cardiac de- compensation	
65 R. R.	Colored Male 45	Hyperten- sive disease of the heart	3/29	53.0	4.9	0	Cardiac de- compensation	

colorimeter. The values for urea nitrogen in this group of patients with marked indicanemia varied from 38.8 to 173 mg. per hundred cubic centimeters and that for creatinine from 2.6 to 15.5 per hundred cubic centimeters of blood.

All of the thirty-one patients in this group showed a marked indicanemia. All died in uremia. Most of them had also marked retentions of nitrogen. But in some (cases 23, 25, 27, 28 and 29) the urea nitrogen and the creatinine were only slightly increased and would not have indicated the presence of grave renal insufficiency. Yet in these the marked accumulation of indican proved more reliable, for these patients died in uremia, despite the low blood nitrogen. It was further shown that the indican reaction announced the imminent danger earlier, was more sensitive to absolute renal insufficiency, than the two other determinations (case 26).

As to clinical diagnosis, these cases included seventeen of chronic diffuse glomerulonephritis, seven of malignant renal sclerosis (primary contracted kidney), two of subacute glomerulonephritis and three of pyelonephritis, hypertrophied prostate and gonorrheal urethral stricture with urinary retention. No case of acute glomerulonephritis was encountered in this group.

In the second group are collected cases which showed no rise or but a slight rise of the blood indican. The reading was between 0.05 and 0.35 mg. per hundred cubic centimeters of blood. In the literature, from 0.05 to 0.15 mg. per hundred cubic centimeters are given as the normal values. The symbol O includes the cases showing from 0.05 to 0.15 mg. and + the cases showing from 0.2 to 0.35 mg. They would correspond to a colorless or faintly purple coloration of the chloroform, to a reading of 15 or less on the Dunning colorimeter. In this group, the urea nitrogen varied from 12.0 to 82 mg. per hundred cubic centimeters of blood, and the creatinine from 1.4 to 5.1 mg.

The thirty-four patients in this group showed an absence of, or a faint, indicanemia. Among these there were eleven (table 5) with high values for urea nitrogen and creatinine, values which would have suggested uremia. Despite this, there was no case of nephritis or other grave renal involvement in this group, and none of the patients died of uremia. The clinical diagnosis and the cause of death as determined independently, with no reference to the observations on indican, are evident from the lists given. Thus, in nonuremic, as well as in uremic conditions, the indican determination surpasses in reliability the blood analysis for urea nitrogen and creatinine.

In group 3, the urea nitrogen values varied from 9.8 to 84 and the creatinine from 1.8 to 8.5 mg. per hundred cubic centimeters of blood. Yet in all these thirty-two patients, the blood indican was normal or but negligibly elevated, and all thirty-two left the hospital markedly improved or completely recovered.

In this "recovery group," the discrepancy between the results of the indican and of the urea nitrogen and creatinine determinations is still more striking than it is in group 2. There were six patients (cases

TABLE 6.—*Absent or Faint Indicanemia with Low or Moderate Urca Nitrogen Values; Recovery*

No.; Pa- tient	Race and Sex	Age	Clinical	Diagnosis	Date, 1929	Blood Chemistry			Result
						Urea, Nitrogen Mg. per 100 Cc. of Blood	Creat- inine	Indi- can	
66 R. O.	Colored Male	50	Hypertensive heart	disease of the	4/15	19.6	1.75	+	Recovery
67 W. C.	White Male	65	Hypertensive heart	disease of the	6/ 1	23.0	1.9	0	Recovery
68 L. O.	White Male	55	Hypertensive heart	disease of the	3/29 4/ 4	32.0 45.0	2.5 ...	0 0	Recovery Recovery
69 J. L.	White Male	50	Hypertensive heart	disease of the	4/ 4	31.0	2.1	+	Recovery
70 O. P.	White Male	51	Hypertensive heart, with arteriosclerosis	disease of the benign renal	2/25	23.0	1.8	0	Recovery
71 N. B.	White Male	49	Hypertensive heart, with arteriosclerosis	disease of the benign renal	3/ 5	30.0	2.2	..	Recovery
72 A. J.	White Male	80	Hypertensive heart, with arteriosclerosis	disease of the benign renal	4/ 2	23.0	1.8	0	Recovery
73 A. S.	White Male	32	Hypertensive heart, with arteriosclerosis	disease of the benign renal	2/ 3	33.0	2.0	..	Recovery
74 J. M.	White Male	59	Hypertensive heart, with arteriosclerosis	disease of the benign renal	3/13	9.8	...	0	Recovery
75 D. H.	Colored Male	54	Hypertensive heart, with arteriosclerosis	disease of the benign renal	3/27	32.7	2.1	0	Recovery
76 N. V.	White Female	39	Syphilitic disease of the heart		3/29	23.0	1.9	0	Recovery
77 E. M.	Colored Female	13	Acute nephritis		3/ 3	9.8	...	0	Recovery
78 W. P.	Colored Male	15	Subacute nephritis		4/15	24.0	2.0	0	Recovery
79 I. M.	White Female	41	Chronic diffuse nephritis....		4/18	37.0	2.5	0	Recovery
80 M. S.	White Female	48	Chronic diffuse nephritis.....		5/21	17.0	...	0	Recovery
81 J. O.	Colored Male	38	Urinary extravasation from a gonorrheal urethral stricture		3/30	29.0	2.0	0	Recovery
82 G. O.	White Male	53	Hypertrophied prostate		3/12	41.0	2.7	..	Recovery
83 G. F.	White Male	75	Hypertrophied prostate		4/22	32.7	2.1	..	Recovery
84 J. D.	White Male	71	Carcinoma of the prostate..		4/12	39.0	3.0	0	On deep roentgen therapy
85 A. T.	White Male	49	Carcinoma of the urinary bladder		4/ 2	34.5	2.2	0	On deep roentgen therapy
86 O. K.	White Male	45	Chronic alcoholism		3/25	28.0	2.2	0	Recovery
87 A. R.	White Male	46	Chronic alcoholism		4/22	46.0	2.9	..	Recovery
88 E. G.	White Female	68	Chronic arthritis		3/26	42.0	2.8	0	Recovery
89 W. S.	White Male	59	Serum sickness		4/ 1	28.5	2.1	0	Recovery
90 E. B.	White Male	39	Chronic bronchitis		3/21	39.7	2.5	0	Recovery

91 to 97) with high urea nitrogen and creatinine values. Yet in these, indicanemia was absent and the patients recovered.

In group 4 are collected the few cases in which the results of the indican determination was doubtful. The readings varied from 1 to 2 mg. per hundred cubic centimeters of blood, a + 2 reaction. This would correspond to an intermediate reaction, a distinct but slight purple discoloration of the chloroform, from 15 to 30 on the Dunning colorimeter. An elevation of urea nitrogen to 30 or 40 mg. would be no more determinate. In these cases a repetition of the test a few days or weeks later yielded the decision. Either the indican went up and the patient died from uremia; or the value remained stationary and

TABLE 7.—*Absent or Faint Indicanemia, with High Urea Nitrogen; Recovery*

No.; Pa- tient	Race and Sex	Age	Clinical Diagnosis	Blood Chemistry				Indi- can	Result
				Date, 1929	Urea, Nitrogen Mg. per 100 Cc. of Blood	Creat- inine			
91 R. N.	White Male	54	Hypertensive disease of the heart; benign renal arterio-sclerosis	3/ 1	62.5	5.0		0	Recovery
92 S. S.	Colored Male	46	Syphilitic disease of the heart	4/27	58.0	4.8		0	Recovery
93 B. S.	White Male	21	Chronic diffuse nephritis....	3/25	50.0	...		0	Recovery
94 R. M.	White Female	29	Acute hemorrhagic nephritis..	4/18	84.0	8.5		0	Recovery
95 M. R.	White Male	63	Hypertrophied prostate	3/27	52.3	2.5		0	Recovery
96 C. M.	White Male	65	Chronic alcoholism	4/27	54.0	3.7		0	Recovery
97 C. C.	Colored Female	23	Stomatitis	4/12	55.5	...		0	Recovery

death from cardiac decompensation or bronchopneumonia terminated the case; or the indican went down and the patient recovered.

CONCLUSIONS

In our series of one hundred and four cases, there was not a single one in which a marked accumulation of indican in the blood (+ 3 and + 4, corresponding to 2.5 to 5.0 mg. per hundred cubic centimeters) failed to announce an approaching uremia or one already present. Were the urea nitrogen and creatinine high or low, a marked indicanemia spelled death in uremia. On the other hand, if the indican reaction were weak or absent, then even in spite of a high urea nitrogen and creatinine value there was no danger of uremia. The patient recovered, or if not, died of myocardial insufficiency, pneumonia, cerebral hemorrhage or any other condition than uremia. We may conclude, then, from this work that the determination of indican in the blood is a sensitive and

specific test of absolute renal insufficiency, that is reliable in diagnosis and in prognosis.

By use of the standards described, indican determinations are established as a quantitative laboratory procedure that is as accurate as the urea nitrogen or creatinine readings. A simplification of the method is described which enables the practitioner to make the determination of blood indican in his own office with adequate accuracy and with a minimum of time and effort.

TABLE 8.—*Intermediate Indicanemia; Uncertain Prognosis*

No.; Patient	Race, Sex and Age	Clinical Diagnosis	Blood Chemistry				Result	(1929)	Postmortem Data
			Date, 1929	Urea Nitrogen, Mg. per 100 Cc. of Blood	Creat- inine	Indi- can +			
98 E. N.	White Male 43	Chronic diffuse nephritis	4/ 6	51.3	3.3	2	Death in uremia	5/27	(P.M. 445) Subacute glomerulo- nephritis (intracapillary)
			4/18	48.0	3.3	3			
			5/ 6	42.0	2.6	4			
			5/22	51.0	2.6	4			
99 L. N.	White Male 23	Subchronic diffuse nephritis	2/24	60.0	4.6	1	Discharged, recovered	4/ 8	
			2/27	100.0	6.3	2			
			3/ 5	27.5	2.0	1			
			3/16	19.0	1.7	2			
			4/ 5	44.0	2.8	0			
100 T. W.	White Male 33	Chronic diffuse nephritis	2/22	80.0	10.0	2	Death in uremia	4/ 1	
			3/22	70.0	8.5	4			
101 A. P.	Colored Male 56	Chronic diffuse nephritis	3/21	62.0	4.4	2	Discharged, recovered	4/ 9	
			4/ 7	43.0	3.0	1			
102 J. T.	White Male 54	Pyelo- nephritis	3/16	51.0	3.0	2	Died of broncho- pneumonia	3/19	
103 C. R.	White Male 77	Hyperten- sive disease of the heart	2/23	21.0	2.0	2	Died of car- diac decom- pensation	3/30	
			2/23	21.0	1.7	1			
104 J. W.	White Female 39	Hyperten- sive disease of the heart	4/17	39.0	2.5	2	Died of car- diac decom- pensation	4/19	

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CAROTINEMIA AND DIABETES

II. THE RELATIONSHIP BETWEEN THE SUGAR, CHOLESTEROL AND CAROTIN CONTENTS OF BLOOD PLASMA *

I. M. RABINOWITCH, M.D.

MONTREAL, CANADA

In a previous communication,¹ I reported the results of an investigation on the phenomenon of xanthosis occurring during the course of diabetes mellitus. The incidence of this condition does not appear to be great. It was found in only fifty-nine of 1,400 diabetic patients, selected at random at the clinic for patients with diabetes in the Montreal General Hospital. The significance of xanthosis was discussed. It was suggested that a diet high in vegetable content to which the diabetic patient is subjected and to which this condition is generally attributed is not the only factor involved. Evidence favoring this view was that thirteen of the fifty-nine patients with this skin condition had never been on special diets prior to its detection, and that, so far as I am aware, it is not found in vegetarians. That it may be of prognostic importance was suggested by the fact that in the group of diabetic patients with this condition the incidence of those requiring insulin was high. Forty-four of the fifty-nine patients with diabetes, that is, an incidence of 74.5 per cent, required this drug; whereas, only 18 per cent of all of the patients in the clinic were using it. The incidence of arteriosclerosis was also high. Thirty-six of the fifty-nine patients, that is, an incidence of 61 per cent, had some evidence of it; whereas, it was present in only 22 per cent of all cases. Apropos of these patients with arteriosclerosis, it may here be mentioned that the average duration of diabetes in these cases was only 3.1 years. Compared with the whole group of diabetic patients, this is a rather short period for one to acquire this complication. Hypercholesterolemia was also a marked feature, but there were difficulties in interpreting this phenomenon. Other features of note were that insulin edema was found in four cases, hyperglycemia difficult to control with insulin in eleven cases, and raised renal threshold for sugar in six cases. In view of these observations, it was suggested that xanthosis occurring during the course of diabetes mellitus indicated an unfavorable prognosis, and its study deserves more consideration than it has been given hitherto.

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* From the Department of Metabolism, the Montreal General Hospital.

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In order to test the correctness of this conclusion it was considered advisable to make a more complete clinical and laboratory study of this phenomenon. Difficulty was at once encountered. When there is well marked xanthosis, that is, when there is the characteristic yellow discoloration of the nasolabial folds, the palms and the soles, its detection is not difficult. Various grades of discoloration are met with, however, and when slight, these may easily be confused with the color of the skin associated with the various anemias and with icterus. It is obvious that the former condition may be ruled out by estimations of the hemoglobin and the latter by estimations of the bilirubin content of the blood by means of the van den Bergh reaction.

In spite of the aforementioned precautions, doubtful cases of xanthosis may be met with. In order to make certain of the presence or absence of this condition, it is necessary to estimate directly the lipochrome content of the blood. For this purpose, estimation of the carotin content only appears to suffice. This is based on the observations of van den Bergh and Snapper,² Bürger and Reinhart,³ Salomon,⁴ Hess and Myers,⁵ Head and Johnson,⁶ Stoner⁷ and Connor.⁸ Chemical and spectroscopic tests support the view that xanthosis is due chiefly to excess quantities of carotin.

Through the efforts of Tswett⁹ and Willstaetter and Mieg,¹⁰ and, later, of Palmer and others¹¹ who made an extensive study of the pigments of biologic materials (milk, butter, eggs, agricultural products), methods for such a study are now available. Carotin can now readily be detected and estimated quantitatively. This depends on three properties of this pigment, namely, its solubilities in alcohol and petroleum-ether, its failure to be adsorbed onto calcium carbonate and its spectroscopic bands.

For routine purposes, excess quantities of carotin in the blood may readily be detected by a method based on the following solubility properties of this and other pigments met with clinically. Hess and Myers, Connor, and also Stoner, employed this principle. The latter, however, did not record the origin of his method.

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3. Bürger and Reinhart: *Deutsche med. Wchnschr.* **45**:430, 1919.

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8. Connor: *Am. J. Path.* **14**:227, 235, 293, 1928.

9. Tswett: *Ber. d. bot. Gesell.* **24**:316, 384, 1906; **29**:630, 1911.

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Palmer and his co-workers stated: "It has been found that carotin cannot be extracted from its solution in low-boiling-point petroleum-ether by 80 to 90 per cent alcohol, while low-boiling-point petroleum-ether will quantitatively extract carotin from its solution in 80 to 90 per cent alcohol."

The observation that carotin can be removed from its solution in alcohol by petroleum-ether has an important bearing on the method used in this study. Much of the carotin in the blood may be bound to the proteins, either chemically or physically (adsorption). In either case, the pigment is readily set free from the proteins by precipitating the latter with 95 per cent alcohol. Of importance also are other blood pigments frequently met with clinically, particularly bile. Some of these are also soluble in alcohol. They remain in the alcohol, however, when the latter is mixed with low boiling point petroleum-ether and the mixture is shaken. For example, even with blood from patients with marked jaundice, showing intense reactions with the van den Bergh test, none of the pigments responsible for this color reaction are removed from the alcoholic fraction of the mixture by the petroleum-ether. Under the same conditions, low boiling point petroleum-ether also fails to remove pigments liberated from hemolyzed blood corpuscles. The following tests readily demonstrate the foregoing phenomena.

To 3 cc. of plasma, containing large quantities of bilirubin or hemolyzed blood, an amount of plaster of paris is added sufficient to bring the mixture to the consistency of a paste. To this is added 3 cc. of 95 per cent ethyl alcohol. The mixture is shaken for a few minutes. When precipitation of the proteins is complete, 3 cc. of petroleum-ether (boiling point from 30-50 C.) is added. The mixture is shaken for ten minutes and then centrifuged. It will be found that all of the bilirubin or hemolyzed blood pigments remain in the alcoholic fraction.

Even in normal subjects, the layer of ether may acquire a yellowish tinge. This, or the greater part of it, is vegetable pigment (carotin). (Practically all normal blood contains minute traces of vegetable pigment. This will be referred to presently.)

If this test is applied to plasma containing large amounts of carotin, all of the latter will be found in the upper, that is, in the ether layer. The solution of carotin in ether may now be removed and placed in a clean dry test tube for purposes of comparison with standards.

For quantitative work in this laboratory a solution of oleic acid in petroleum ether¹² is used, and the results are expressed in terms of units. By the foregoing method, the maximum amount of pigment found in the

12. This solution does not keep well. It is renewed weekly. For a permanent standard, potassium bichromate may be used, as recommended by Connor (*J. Biol. Chem.* **77**:619, 1928).

blood of more than 100 normal subjects gave a color corresponding to that of a 10 per cent solution (by volume) of oleic acid. This is regarded as one unit of pigment.

This report concerns the results of an investigation of the bloods of 500 patients with diabetes selected at random. In each case the following analyses were made on the same sample: (1) sugar; (2) cholesterol; (3) bilirubin (van den Bergh test) and (4) carotin.

An attempt was first made to determine the different degrees of carotinemia and their incidences. The results are shown in table 1. It

TABLE 1.—*Degrees of Carotinemia Found Among Five Hundred Diabetic Patients and Their Incidences*

Carotin (Units)	Incidence
1.....	74
2.....	98
3.....	98
4.....	74
5.....	59
6.....	65
7.....	16
8.....	9
9.....	3
10.....	2
11.....	2

TABLE 2.—*Absence of Relationship Between Sugar and Carotin Content of Blood*

Carotin (Units)	Blood Sugar (per Cent)		
	High	Low	Average
1.....	0.416	0.084	0.174
2.....	0.555	0.090	0.202
3.....	0.295	0.091	0.167
4.....	0.454	0.063	0.167
5.....	0.434	0.091	0.174
6.....	0.588	0.074	0.178
7.....	0.454	0.116	0.226
8.....	0.285	0.103	0.192
9*	0.250	0.149	
10*	0.143	0.109	
11*	0.400	0.204	

* The incidences of these concentrations of carotin were too low to attach significance to the data.

will be observed, as pointed out in my first report,¹ that most diabetic patients have more pigment than do normal subjects. Only seventy-four, that is, about 15 per cent of the total number of patients observed had quantities within the normal limits. The great majority had between 1 and 5 units. This amount is apparently insufficient to produce obvious xanthosis. All of the fifty-nine patients with xanthosis, detected clinically and without laboratory aid, had 6 units or more of this pigment.

An attempt was then made to determine whether there was a relationship between sugar and carotin contents of blood. No relationship was found. This is shown in table 2. These results are those one would, *a priori*, expect if there is a relationship between prognosis and

carotinemia, since, as is generally known, prognosis and sugar content of blood are not related. An analogy may be found in cholesterol studies. Prognosis and plasma cholesterols are related;¹³ yet there is no relationship between the latter and blood sugar. This is shown in table 3.

These results led to an investigation, the importance of which is obvious from the following: If both plasma cholesterol and carotin are related to prognosis, one would expect to find some relationship between carotin and cholesterol. Such a relationship was found.

In the interpretation of these observations there are two important considerations. A large number of diabetic patients have disease of the biliary passages. This has been shown in Joslin's clinic as well as in the one at the Montreal General Hospital.¹⁴ In cases of disease of the biliary passages the cholesterol content of the blood may be increased. As a matter of fact, the blood of eleven of fifty-nine patients with

TABLE 3.—*Absence of Relationship Between Sugar and Cholesterol Contents of Blood in Five Hundred Cases of Diabetes Mellitus*

Blood Sugar, per Cent	Number of Cases	Average Cholesterol, per Cent
0.120.....	120	0.312
0.121-0.200.....	228	0.290
0.201-0.250.....	65	0.286
0.251-0.300.....	37	0.260
0.301-0.350.....	21	0.292
0.351-0.400.....	11	0.351
0.401-0.450.....	3	0.241
0.451-0.500.....	4	0.342
0.500.....	3	0.261

xanthosis gave positive van den Bergh reactions. This test, when positive, as is well known, is a reliable indication of biliary disease in the absence of hemolytic processes. Such cases should, obviously, be excluded from this study. This, it may be noted, was done in the first investigation.¹ The results, however, did not affect the average. In fact, the highest cholesterol value was found in the absence of a positive van den Bergh reaction, namely, 0.56 per cent.

The data showing relationship between cholesterol and carotin contents of blood are briefly summarized in table 4. Here are recorded the high, low and average cholesterol values corresponding to the different degrees of carotinemia. It will be observed that as the degree

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of carotinemia increases, the average cholesterol also increases, but not to the same extent.

In order to determine whether the differences noted between the different groups were significant, the data were treated statistically. For this purpose the following values were calculated for each of the aforementioned groups: (a) number of cases; (b) average cholesterol (mean) (c) standard deviation; and (d) probable error of the mean.

With this information it is possible to determine whether the difference obtained between the means of any two groups one wishes to compare are significant or merely the result of chance. Comparisons were made between the following groups: 1 and 2; 2 and 3; 3 and 4;

TABLE 4.—*Statistical Demonstration of the Relationship Found Between the Cholesterol and Carotin Contents of Blood in Five Hundred Cases of Diabetes Mellitus*

Units Caro- tin	Number of Patients	Plasma Cholesterol, per Cent			Standard Devia- tion	Probable Error of Mean	Probable Error of Difference Between Means	Differ- ence Between Means	Difference Probable Error of Difference
		High	Low	Arith- metical Mean					
1	74	0.354	0.109	0.209	62.6	4.91			
2	98	0.666	0.078	0.243	45.6	3.10	5.8	34	5.8
3	98	0.833	0.181	0.270	82.1	5.59	6.4	27	4.2
4	74	0.800	0.133	0.304	102.8	8.05	9.7	34	3.5
5	59	0.483	0.147	0.309	85.0	7.50	11.0	5	0.45
6	65	0.794	0.177	0.364	151.7	12.60	14.7	55	3.7
7	16	0.793	0.191	0.469	307.7	51.84	53.3	105	1.9
8	9	0.980	0.297	0.487	208.4	46.80	69.0	18	0.26

4 and 5; 5 and 6; 6 and 7, and 7 and 8. The number of observations in the remaining group were too small to allow for conclusions.

The necessary further calculations were as follows: (a) the difference between the means of the groups to be compared; (b) the probable error of the difference, and (c) the ratio of the difference to the probable error of the difference.

The results of these calculations are shown in table 4.

It will be seen (last column) that with the exception of the differences noted between groups 4 and 5, and groups 7 and 8, there is statistical proof that the differences noted between the means of the different groups compared were not accidental. In other words, carotin and cholesterol are related.

It may here be observed that the lowest ratios obtained included the groups which had the least number of subjects. In view of the small number of observations, limited significance could be attached to these ratios in any event.

These results led to certain observations. Since plants contain substances (sterols) allied chemically to cholesterol, is it not possible that herein lies the explanation of the correlation found? That this is not the only explanation, however, is suggested by the fact that some subjects had enormous quantities of carotin and at the same time had normal cholesterol values, and, conversely, a number of persons had excessive quantities of cholesterol and practically normal amounts of carotin. Thus (table 4):

Cholesterol (%)	Carotin (units)
0.666	2
0.191	7

Numerous similar examples were met with in this series.

SUMMARY

It would appear that for some unknown reason certain diabetic patients retain ingested vegetable pigments to a greater extent than others. The importance of this observation is that such persons usually do not appear to do well clinically, and the majority have a high cholesterol content of the blood. Though large amounts of carotin may be responsible for high values of plasma cholesterol because of their chemical relationship, this does not appear to be the only cause. Since there is a relationship between cholesterol and carotin and in view of the unfavorable prognosis for patients with high cholesterols, it is suggested that marked carotinemia also suggests an unfavorable prognosis.

As with cholesterols, there are exceptional cases. In such instances it was found that carotin may accumulate in the blood rapidly and yet no other evidence of downward progress may be noted. Both of these phenomena require further study. These exceptions do not alter the value of studies of the cholesterol content in the majority of cases; neither should they, therefore, do so in the cases of carotin.

Since cholesterol and carotin contents of blood do not always parallel each other, it is reasonable to assume that there are two different factors involved, though in a great majority of cases both of them probably operate. To elucidate the picture further, time and careful clinical studies are necessary. The purpose of the foregoing report is to demonstrate the probability that carotinemia has a greater clinical significance in diabetes mellitus than that generally attached to it, and to prompt further study of this phenomenon by others, particularly those interested in diabetes. The treatment of patients with diabetes, much more satisfactory as it may be today compared with the past, is far from ideal. The degree of approach can be only in direct proportion to the knowledge concerning the different phases of the disease.

This work was done with the technical assistance of Miss Helen MacGachen, Miss Helen Chisholm and Miss Mary Beard.

ORTHOPNEA

ITS RELATION TO THE INCREASED VENOUS PRESSURE OF MYOCARDIAL FAILURE *

A. CARLTON ERNSTENE, M.D.

AND

HERRMAN L. BLUMGART, M.D.

BOSTON

The factors that impel patients with myocardial failure of the congestive type to sit up in bed in order to breathe more comfortably have aroused the curiosity of many investigators. Numerous theories of the pathogenesis of orthopnea have been advanced, but none completely accounts for all the characteristics of the phenomenon.

REVIEW OF THE LITERATURE

The earlier writers generally believed that the sitting posture was assumed because the accessory muscles of inspiration could then be used to greater advantage. Hofbauer,¹ however, showed that the chief respiratory difficulty in orthopneic patients was expiratory rather than inspiratory, and that the accessory muscles of expiration did not function more efficiently in the upright posture. According to him,² the orthopneic position provides relief because it secures the following mechanical advantages: 1. The lower position of the diaphragm and the consequent increased capacity of the thorax increases the elastic tension of the lungs and so facilitates expiration. The observation of Aron³ that the negative intrathoracic pressure is greater in the sitting than in the recumbent posture supports this hypothesis. 2. The increased negative intrathoracic pressure in the upright position also aids the right ventricle in maintaining blood flow through the lungs. 3. In the recumbent position, the abdominal viscera, by falling against the vertebral column and the posterior half of the diaphragm, not only

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* From the Thorndike Memorial Laboratory, Boston City Hospital, the Medical Research Laboratories, Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

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1. Hofbauer, L.: Ursachen der Orthopnoe, *Ztschr. f. klin. Med.* **61**:389, 1907.

2. Hofbauer, L.: Ursachen der Orthopnoe: II. Die kardiaale Orthopnoe, *Ztschr. f. klin. Med.* **79**:128, 1914.

3. Aron, E.: Ueber einen Versuch den intrapleurale Druck am lebenden Menschen zu messen, *Virchows Arch. f. path. Anat.* **126**:517, 1891.

interfere with diaphragmatic movements but also diminish the aperture of the quadrilateral foramen and so obstruct the return of blood in the inferior vena cava. 4. The abdominal muscles exert an efficacious pumping action on the viscera and inferior vena cava only in the upright position. Hofbauer² asserted that cardiac orthopnea could be explained completely on this purely mechanical basis.

Bohr⁴ found a decrease in the vital capacity, reserve air, and middle capacity of the lungs and an increase in the complemental air in the recumbent as compared with the sitting posture. Rubow⁵ demonstrated that in patients with myocardial failure there is a relative increase in the middle capacity and believed that the orthopneic position is assumed in order to obtain the greatest possible total and middle capacity of the lungs. He believed that any increase in the middle capacity diminishes the resistance to blood flow in the pulmonary capillaries by reducing the tortuosity of these vessels.

Christie and Beams⁶ recently reported that the average vital capacity of the lungs of 290 normal people while lying was 5.5 per cent less than while sitting. Nine patients with orthopnea of necessity with an average reduction of 69.5 per cent from the estimated normal vital capacity of the lungs lost an additional 26.7 per cent on lying down.⁷ Fourteen patients with orthopnea of choice with an average reduction of 55 per cent lost an additional 12.5 per cent on lying down. Nineteen patients with diminished vital capacities, but without orthopnea, had an average reduction of 36 per cent of the estimated normal and lost only an additional 4.7 per cent on lying down. Christie and Beams⁷ believed that the increased vital capacity of the lungs in the upright position is the primary factor in the production of orthopnea.

Haldane, Meakins and Priestley⁸ showed that even in healthy persons the recumbent position accentuates the unevenness with which the lungs normally expand and so tends to produce anoxemia. This tendency in normal persons is partly counteracted by deeper inspiration, a compensatory mechanism not available to patients suffering from

4. Bohr, C.: Die funktionellen Aenderungen in der Mittellage und Vitalkapazität der Lungen, *Deutsche Arch. f. klin. Med.* **88**:385, 1907.

5. Rubow, V.: Die kardiale Dyspnoe, *Ergebn. d. inn. Med. u. Kinderh.* **3**:71, 1909.

6. Christie, C. D., and Beams, A. J.: The Estimation of Normal Vital Capacity, with Especial Reference to the Effect of Posture, *Arch. Int. Med.* **30**:34 (July) 1922.

7. Christie, C. D., and Beams, A. J.: Orthopnea, *Arch. Int. Med.* **31**:85 (Jan.) 1923.

8. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: The Effects of Shallow Breathing, *J. Physiol.* **52**:433, 1919.

congestive failure. Consequently, in congestive failure, the mixed arterial blood leaving the lungs is less well oxygenated in the recumbent than in the sitting position, and the respiratory center therefore is exposed to increased anoxemia. If the patient sits up, however, the lungs expand more evenly, the anoxemia is diminished, and the partial asphyxia of the respiratory center is lessened. Haldane, Meakins and Priestley believed that their observations explain the occurrence of orthopnea in myocardial failure.

Recently, Wilson,⁹ apparently unacquainted with the work of Bohr,⁴ reinvestigated the effect of posture on the volume of the reserve air of the lungs in normal persons and found a marked reduction in the recumbent as compared with the erect position. He believed this decreased volume of the reserve air in the recumbent position led to a diminution in the oxygen content of the mixed arterial blood leaving the lungs. His explanation for orthopnea is therefore closely related to that of Haldane, Meakins and Priestley.⁸

Sahli¹⁰ stated that the accessory muscles of respiration can be used to advantage only in the upright posture, and that this position may relieve the diaphragm from the pressure due to fluid within the abdomen. He also stated that the venous congestion of the brain and particularly of the respiratory center was possibly relieved in the sitting position by the action of gravity, and that the accumulation of blood in the lower extremities in this position diminished pulmonary congestion and decreased the work of the heart. He offered no data in support of these hypotheses. Hill¹¹ also believed pulmonary congestion to be diminished in the orthopneic position because of drainage by gravity of a large quantity of blood into the splanchnic area.

Field and Bock,¹² in 1925, found that the average minute volume output of the heart in the sitting position was 76 per cent, and in the upright position only 50 per cent, of that in the recumbent posture. They believed that an accumulation of blood in the legs and splanchnic area occurs in the sitting and standing positions, and that the resultant diminished venous return to the heart leads to decreased cardiac output and lessened pulmonary congestion. Similar observations on the minute volume output of the heart have been reported by several other

9. Wilson, W. H.: The Influence of Posture on the Volume of the Reserve Air, *J. Physiol.* **64**:54, 1928.

10. Sahli, H.: *Lehrbuch der klinischen Untersuchungsmethoden*, ed. 1, Leipzig, Franz Deuticke, 1894.

11. Hill, L.: The Influence of the Force of Gravity on the Circulation. *J. Physiol.* **18**:15, 1895.

12. Field, H., Jr., and Bock, A. V.: Orthopnoea and the Effect of Posture upon the Rate of Blood Flow, *J. Clin. Investigation* **2**:67, 1925.

investigators¹³ using the same method or the ethyl iodide method of Henderson and Haggard.¹⁴ Grollman,¹⁵ however, using the nitrous oxide method of Marshall and Grollman,¹⁶ found a practically constant circulatory minute volume in the recumbent, sitting and standing positions and attributed the differences observed by previous workers to errors inherent in the methods employed.

A NEW HYPOTHESIS OF ORTHOPNEA

We believe that the orthopneic position benefits the patient with congestive circulatory failure because it secures a maximum blood flow about the respiratory center and thereby relieves the patient from the distress due to partial asphyxia in that area. The mechanism of this is conceived to be as follows. Physiologic investigations¹⁷ indicate that the blood flow in the capillaries is dependent on the pressure gradient in these vessels. The greater the difference in pressure along the capillary, the greater the blood flow. An elevation of the venous pressure, therefore, diminishes capillary blood flow in the absence of any striking increase in arteriolar blood pressure. Other factors remaining equal, increased venous pressure leads to stagnation of blood in the capillaries and so produces stagnation anoxemia. It is well known¹⁸ that in myocardial failure the peripheral venous pressure is increased roughly in proportion to the degree of decompensation.

The orthopneic position, in our opinion, relieves the respiratory center of the increased pressure within the veins of that area in the following manner. There are no efficient valves in the veins between the cerebral capillaries and the right auricle.¹⁹ If a patient with uncomplicated cardiovascular failure and a venous pressure at the right auricle equivalent to 15 cm. of water lies flat in bed, there is a corresponding

13. Henderson, Y., and Haggard, H. W.: The Circulation and Its Measurement, *Am. J. Physiol.* **73**:193, 1925. Lawrence, J. S.; Hurxthal, L. M., and Bock, A. V.: Variations in Flow with Changes in Position in Normal and Pathologic Subjects, *J. Clin. Investigation* **3**:613, 1927. Rosen, I. T., and White, H. L.: The Relation of Pulse Pressure to Stroke Volume, *Am. J. Physiol.* **78**:168, 1926. Turner, A. H.: Circulatory Minute Volumes of Healthy Young Women in Reclining, Sitting and Standing Positions, *Am. J. Physiol.* **80**:601, 1927.

14. Henderson and Haggard (footnote 13, first reference).

15. Grollman, A.: The Effect of Variations in Posture on the Output of the Human Heart, *Am. J. Physiol.* **86**:285, 1928.

16. Marshall, E. K., and Grollman, A.: A Method for the Determination of the Circulatory Minute Volume in Man, *Am. J. Physiol.* **86**:117, 1928.

17. Bayliss, W. M., and Starling, E. H.: Observations on Venous Pressures and Their Relationship to Capillary Pressures, *J. Physiol.* **16**:159, 1894.

18. Eyster, J. A. E., and Middleton, W. S.: Clinical Studies on Venous Pressure, *Arch. Int. Med.* **34**:228 (Aug.) 1924.

19. Hill, L.: *Physiology and Pathology of the Cerebral Circulation*, London, J. & A. Churchill, 1896.

pressure of 15 cm. of water in the veins about the respiratory center (fig. 1). This results in diminished blood flow in the capillaries and stagnation anoxemia in this region. If, however, the patient sits up, so that the respiratory center is 15 cm. above the right auricle, the pressure in the veins about the center is zero (fig. 2). The blood flow in the capillaries leading to these veins would then be increased, the respiratory center would receive a more adequate supply of blood, and the subjective respiratory distress would be relieved.

METHOD

To test the validity of this hypothesis, the following studies were undertaken:

Relation between Height of Venous Pressure and Degree of Orthopnea.—If the foregoing hypothesis is valid, one might expect that the degree of orthopnea would closely parallel the degree to which the venous pressure is increased. It is, of course, impossible to measure the venous pressure of the vessels about the respiratory center, but



Fig. 1.—The relation between the pressure in the right auricle and in the veins about the respiratory center, in the recumbent position. In the recumbent position, the right auricle and the respiratory center are in approximately the same horizontal plane. The pressure in the veins about the respiratory center, therefore, is the same as that in the right auricle.

Weed and Hughson²⁰ have shown that, in cats and dogs, brachial and cerebral venous pressures are identical in the recumbent position. In the present investigation, the relation between the height of the systemic venous pressure and the degree of orthopnea was studied in a series of patients with uncomplicated myocardial failure. The venous pressure was measured by the direct venipuncture method of Moritz and Tabora,²¹ using the median basilic or median cephalic vein. The pressure was measured in the recumbent position, unless the patient was unable to endure the discomfort. A minority of the measurements were taken,

20. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by Intravenous Injections of Solutions of Various Concentrations, *Am. J. Physiol.* **108**:101, 1921.

21. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsche Arch. f. klin. Med.* **98**:475, 1910.

therefore, with the patient somewhat elevated. All observations were made with the arm resting at the level of the right auricle. The first measurements were made as soon as possible after the patients were admitted to the hospital, and subsequent observations were carried out at intervals of from three to five days. Successive measurements of venous pressure on each patient were taken at the same time of day, usually between 2 and 4 o'clock in the afternoon, in order to avoid

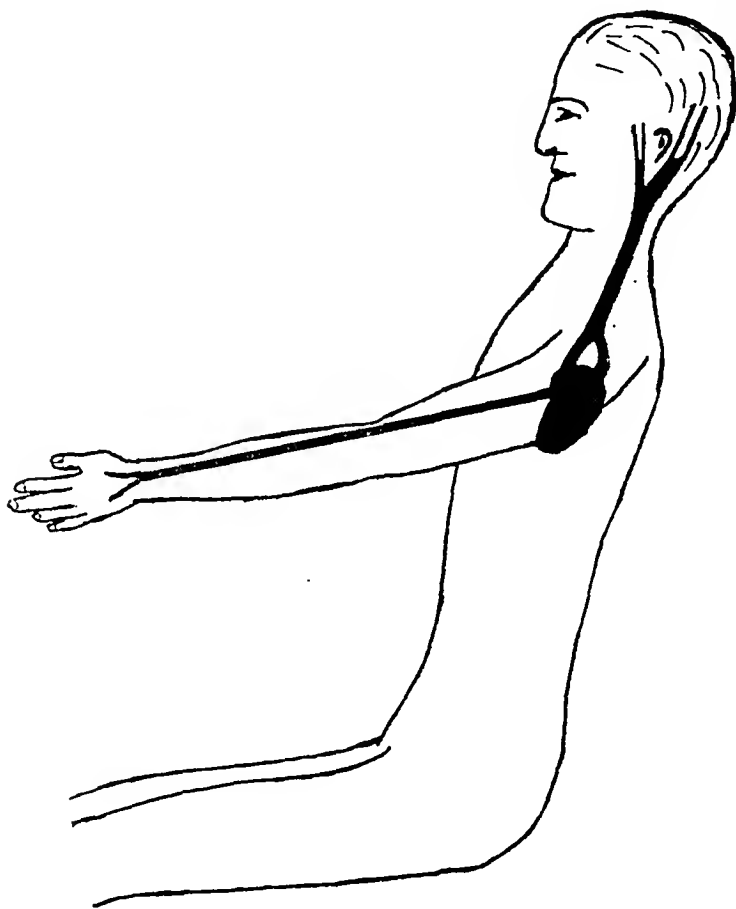


Fig. 2.—The relation between the pressure in the right auricle and in the veins about the respiratory center, in the sitting position. When the patient assumes a sufficiently elevated position, the respiratory center is above the level of the meniscus of the column of venous blood extending upward from the right auricle. The pressure in the veins about the respiratory center, therefore, becomes zero.

the error incident to diurnal fluctuation of the pressure.²² Other precautions outlined by previous investigators,²³ were observed in making

22. Hooker, D. R.: Observations on the Venous Blood Pressure in Man, *Am. J. Physiol.* **35**:73, 1914.

23. Eyster, J. A. E.: Venous Pressure and Its Clinical Applications, *Physiol. Rev.* **6**:281, 1926. Runge, H.: Ueber den Venendrucke im Schwangerschaft. Geburt und Wochenbett, *Arch. f. Gynäk.* **22**:142, 1924.

the measurements of the venous pressure. The degree of orthopnea was ascertained by measuring the perpendicular distance between the level of the right auricle and a point corresponding to the respiratory center, namely the external occipital protuberance. These measurements were made in the evening after the wards had been darkened, and the patients had had an opportunity to assume the most comfortable position for the night. Sedatives were withheld until these observations were finished, in order not to influence the sensitivity of the respiratory center. In estimating the venous pressure and the degree of orthopnea, the position of the right auricle was ascertained in the following manner: With the patient in the recumbent posture, the right auricle is 5 cm. below the fourth chondrosternal junction,²¹ while with the patient sitting at an elevation of 90 degrees, both are at the same level. At all intermediate positions of the patient, the difference between the level of the right auricle and the fourth chondrosternal junction would range between zero and 5 cm. Thus, at an elevation of 45 degrees, the auricle was assumed to be 2.5 cm. below the plane of the fourth chondrosternal junction. The points taken to represent the level of the right auricle and the respiratory center were not, of course, anatomically precise, but nevertheless, were satisfactory for purposes of comparison. The same points were used in the successive observations on the same person, so that any absolute errors would tend to cancel out.

Flexion of the Head.—Previous theories of orthopnea have stressed the significance of changes within the chest or abdomen, whereas the present theory places more emphasis on the importance of the elevation of the head. It therefore seemed that the relative importance of these different factors could be differentiated by elevating the head without elevating the abdomen or thorax. Accordingly, all orthopedic patients were placed in the recumbent position, and as soon as they became acutely distressed the head was flexed forward, care being taken not to alter the position of the thorax. The degree of respiratory distress was observed, and the patient was encouraged to describe any differences in his subjective sensations.

Vital Capacity of the Lungs.—Because previous investigators had stressed the importance of the vital capacity of the lungs in the pathogenesis of orthopnea, the vital capacity was recorded in the orthopneic position at the time of each observation, and whenever feasible, in the recumbent position, both with the head flat and with the head flexed on the chest. The theoretical normal vital capacity of each patient was estimated according to his surface area,²⁴ and from this the percentage

24. West, H. F.: Clinical Studies on the Respiration: VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. 25:306 (March) 1920.

reduction observed in the sitting position was calculated. For example, a man whose surface area is 1.7 square meters has an estimated normal vital capacity of 4,250 cc. If the actually observed vital capacity is 2,000 cc., there is a reduction from the estimated normal of 52.9 per cent.

RESULTS

Relation between Height of Venous Pressure and the Degree of Orthopnea.—Eighty-two measurements of the venous pressure and the perpendicular distance between the occipital protuberance and the level of the right auricle were made in twenty-two patients. A

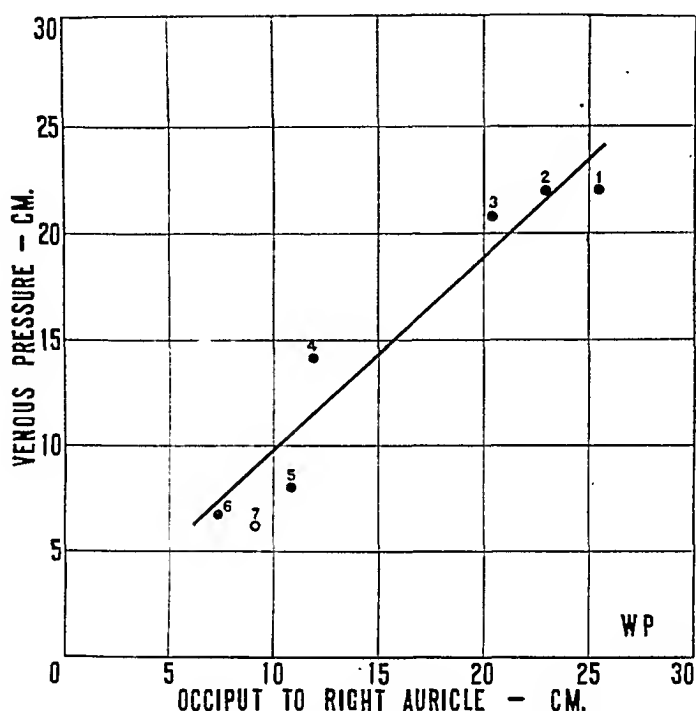


Fig. 3.—Comparisons of the height of venous pressure and the degree of orthopnea in patient W. P. Sequence of measurements is indicated by the numbers above the dots. The open dot (no. 7) indicates the absence of orthopnea of necessity, although orthopnea of choice still was present.

parallelism between the height of venous pressure and the degree of orthopnea was observed. In general, the higher the venous pressure, the greater the orthopnea. Figure 3 shows the results obtained in a typical case. On admission to the hospital, this patient had advanced myocardial failure; the venous pressure was 22 cm. and the degree of orthopnea 25.5 cm. Subsequent observations were made at four day intervals, and the consecutive measurements are represented by the numbered dots in the figure. During the first eight days the venous pressure and the degree of orthopnea diminished only slightly; but with clinical improvement following venesection of 500 cc. of blood,

both decreased rapidly and approximately to the same degree. At the time of the seventh measurement, the venous pressure was 6.1 cm., and orthopnea of necessity had disappeared. The patient no longer experienced respiratory distress in the recumbent position, but still assumed a slightly elevated posture when left to himself. Figure 4 presents the eighty-two comparisons of venous pressure and degree of orthopnea in all patients studied. The degree of orthopnea varied from 4.7 to 25.5 cm. The venous pressure readings falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses in the figure. There is a considerable spread of

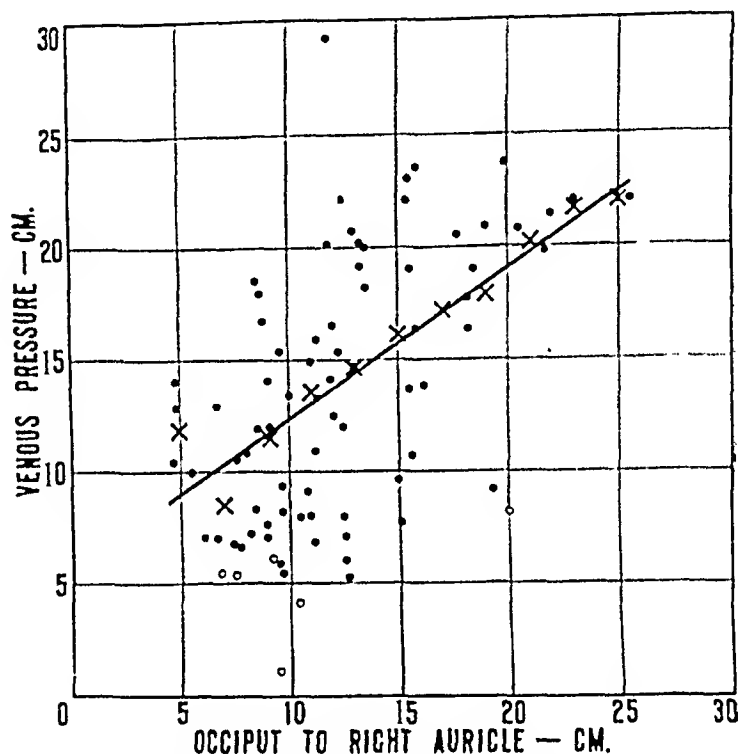


Fig. 4.—Comparisons of the height of venous pressure and the degree of orthopnea. A composite chart. Open dots represent measurements taken after orthopnea of necessity had disappeared although orthopnea of choice still was present. The venous pressure readings falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses.

the individual measurements, but the close parallelism between average venous pressure and degree of orthopnea strongly supports the hypothesis.

Flexion of Head on the Thorax in the Recumbent Position.—Simple elevation of the head by flexion of it on the thorax when the patient was flat in bed produced a conspicuous diminution of respiratory distress in all but one instance. As might be expected, this relief usually was only partial. The one exception was a patient with a venous pressure of 23 cm., who obtained only slight relief in the 90 degree sitting

position and was much more comfortable when leaning forward and supporting himself with his hands. Because of weakness, he was unable to maintain the latter position for long periods and usually remained at an elevation of about 60 degrees. It is of interest that in the more comfortable position of sitting forward, the distance from the external occipital protuberance to the right auricle was 32.5 cm., whereas in the less comfortable upright position of 60 degrees the distance was 19.5 cm.

Vital Capacity of the Lungs.—In order to be certain that the relief experienced by the subjects on flexion of the head was not due to an increase in the vital capacity of the lungs, measurement of the latter was made with the head level with the rest of the body and with the head flexed. In one fourth of the observations (table) the vital capacity was unchanged, while in the others it was either diminished by as much as 200 cc. or increased by as much as 250 cc. Since the subjects experienced relief regardless of a diminution or an increase in the vital capacity, this factor must be considered of small importance. For the entire group, the vital capacity in the position with the head flexed showed an average increase of 14 cc.

Since other observers have attributed the increased comfort obtained in the sitting position to an increase in the vital capacity of the lungs, the latter was measured, whenever possible, in both the recumbent and the upright position. Sixty-three comparisons of the vital capacity in the two positions were made in eighteen subjects. The results obtained (table) do not corroborate the observation of Christie and Beams⁷ that there is an important further reduction of the already greatly diminished vital capacity of the lungs in patients with orthopnea of necessity when they assume the recumbent position. Christie and Beams, in nine observations on nine patients with orthopnea of necessity, observed that the vital capacity averaged 26.7 per cent less on lying down. In sixty-three measurements on eighteen similar patients, we found the vital capacity averaged only 8.3 per cent less in the recumbent position. The decrease ranged from zero to 23.9 per cent of the vital capacity in the sitting position, but was less than 5 per cent in twenty-two of the sixty-three observations. In seven observations there was no change, while in only three did the decrease amount to 20 per cent or more. In these sixty-three measurements, the average vital capacity in the orthopneic position was 41.6 per cent of the estimated normal. These results are not strictly comparable with those of Christie and Beams since, in the present series, the vital capacities in the sitting posture were measured at the elevation which the patients regarded as most comfortable, while Christie and Beams apparently recorded the values for the 90 degree position. Our studies demon-

strate that orthopnea of necessity does occur in patients who do not show a great reduction of the vital capacity of the lungs on changing from the sitting to the recumbent posture.

To gain further knowledge of the importance of the vital capacity of the lungs in the mechanism of orthopnea, the percentage reduction of the vital capacity in the sitting position was compared with the perpendicular distance between the occipital protuberance and the level of the right auricle (figure 5). In striking contrast to the definite correlation between the venous pressure and the degree of orthopnea, no close relationship was apparent between the reduction in the vital capacity of the lungs and the degree of orthopnea. While both orthopnea

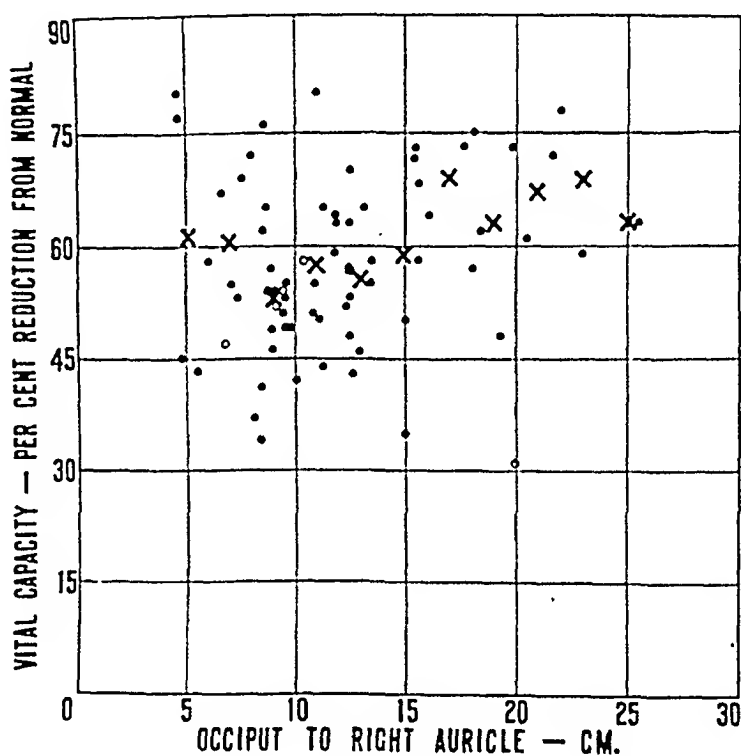


Fig. 5.—Comparisons of the percentage reduction of the vital capacity of the lungs and the degree of orthopnea. A composite chart. Open dots represent measurements taken after orthopnea of necessity had disappeared, although orthopnea of choice still was present. The percentages of reduction of the vital capacity falling within each 2 cm. of orthopnea of necessity were averaged, and these averages are represented by the crosses.

of necessity and a greatly reduced vital capacity occur in advanced congestive failure, no parallelism between the two is evident. Hence, the extent of the diminution of the vital capacity does not appear to play an important rôle in determining the degree of elevation which gives the patient maximum relief. Thus in the case of W. P. (table), the vital capacity during the first twelve days remained practically unchanged. During this time the orthopnea of necessity diminished one half, and the venous pressure decreased from 22 to 14.1 cm.

Summary of Observations on Venous Pressure, Vital Capacity of the Lungs, and Degree of Orthopnea

Sub- ject	Age	Diagnosis	Date	Venous Pressure, Cm. of Water	Occipital Protuber- ance to Right Auricle, Cm.	Vital Capacity						
						Estimated Normal, Cc.	In Orthop- neic Position, Cc.	Reduction from Normal, per Cent	In Recum- bent Position with Head Flat, Cc.	Decrease from Orthopneic Position, per Cent	Change on Elevating Head, Cc.	Comment
W. P.	54	Arteriosclerotic heart disease, auricular fibrillation	8/ 2/27	92.0	25.5	4,450	1,050	63	1,500	9.1	+50	
			8/ 6/27	22.0	23.0	1,800	59	1,650	8.3	0	
			8/10/27	20.7	20.5	1,750	61	1,625	7.1	+25	
			8/14/27	14.1	11.9	1,650	63	1,450	12.1	0	
			8/18/27	8.0	10.9	2,000	55	1,925	3.8	0	
			8/22/27	6.7	7.4	2,100	53	1,900	9.5	0	
8/26/27	6.1	9.2	2,150	52	1,975	8.1	-75	No orthopnea of necessity			
P. G.	66	Arteriosclerotic heart disease, auricular fibrillation	8/11/27	19.1	13.3	Patient uncooperative; no studies of vital capacity	
			8/15/27	7.0	6.7		
			8/20/27	6.6	7.7		
8/25/27	5.3	7.5	No orthopnea of necessity				
S. K.	14	Rheumatic heart disease, mitral stenosis, auricular fibrillation	8/11/27	13.7	15.5	No studies of vital capac- ity	
				
S. L.	35	Rheumatic heart disease, mitral stenosis, auricular fibrillation	8/25/27	9.9	5.5	3,040	1,725	43	1,650	4.4	-25	
			8/28/27	12.8	4.8	1,675	45	1,675	0.0	0	
			9/ 1/27	13.4	10.1	1,750	42	1,650	5.7	-25	
			9/ 4/27	13.3	11.3	1,700	44	1,700	0.0	+75	
			9/ 8/27	14.0	9.0	1,650	46	1,625	1.5	0	
			9/ 9/27	14.0	4.7	3,060	600	80	550	8.3	0	
9/12/27	14.9	11.0	600	80	525	12.5	+50				
9/15/27	11.9	8.6	725	75	700	3.5	0				
9/19/27	10.7	8.0	850	72	700	17.6	0				
9/23/27	10.4	4.7	700	77	300	14.3	0				
9/27/27	10.5	7.6	950	69	950	0.0	0				
10/ 1/27	17.9	8.7	1,050	65	925	11.9	+75				
A. W.	30	Rheumatic heart disease, mitral stenosis	9/19/27	6.0	12.5	4,300	1,275	70	1,225	3.9	0	
			9/23/27	6.8	11.1	1,800	58	1,800	0.0	-25	
			9 27 27	4.1	10.4	-25	
R. W.	63	Arteriosclerotic heart disease	9/19/27	6.0	12.5	4,300	1,275	70	1,225	3.9	0	No orthopnea of necessity
			9/23/27	6.8	11.1	1,800	58	1,800	0.0	-25	
9 27 27	4.1	10.4	-25			

P. L.	41	Rheumatic heart disease, mitral stenosis, auricular fibrillation	11/ 3/27 11/ 6/27 11/10/27 11/14/27 11/17/27 11/21/27 11/28/27 12/ 6/27 12/12/27 12/16/27 12/20/27 12/28/27	20.1 22.0 19.0 18.9 13.8 20.8 22.1 10.7 19.7 20.5 23.7 16.3	11.8 15.4 18.4 15.6 16.2 10.0 12.5 15.6 21.7 17.7 19.8 18.2	4.150	1.600 1.300 1.700 1.825 1.600 1.675 1.650 1.450 1.250 1.200 1.225 1.125	64 71 62 58 61 63 63 68 72 73 73 75	1.300 1.300 1.525 1.675 1.500 1.300 1.525 1.300 1.000 1.050 1.100	18.8 0.0 10.3 8.2 0.2 10.4 7.6 10.3 20.0 12.5 10.2	0 +25 +25 0 -25 +50 -25 +50 +50 +50 -25	
H. B.	53	Arteriosclerotic heart disease	12/16/27 12/20/27 12/21/27 12/28/27 1/ 2/28	12.0 7.6 11.6 9.3 5.4	6.7 8.9 9.1 9.7 6.8	5.180	1.725 2.250 2.375 2.350 2.725	67 57 54 55 47	1.450 2.075 2.325 2.250 2.575	16.0 7.8 2.1 4.3 5.5	+250 +25 -25 -50 +50	No orthopnea of necessity
E. S.	68	Arteriosclerotic heart disease, auricular fibrillation	12/21/27 12/26/27	7.2 8.3	8.2 8.4	4.525	2.875 3.000	37 31	2.750 2.850	4.3 5.0	+25 0	
H. W.	60	Arteriosclerotic heart disease, auricular fibrillation	12/31/27 1/ 2/28 1/ 6/28 1/ 9/28 1/13/28	7.0 5.4 7.0 9.1 8.2	10.5 9.7 8.9 10.8 9.7	4.250 2.130 2.150 2.075 2.150	.. 49 19 31 49 1.050 2.125 1.950 2.050 9.3 1.2 6.0 4.7 +50 +25 +100 -50	No measurement of vital capacity because of coughing
D. B.	72	Arteriosclerotic heart disease, angina pectoris	1/ 2/28	12.5	12.1	1.300	..	1.050	12.5	+50	
J. R.	62	Arteriosclerotic heart disease, auricular fibrillation, angina pectoris	1/ 4/28 1/ 7/28 1/10/28 1/15/28	15.9 14.7 7.0 1.1	11.3 13.0 6.1 9.5	4.900	1.700 1.700 2.050 2.350	65 65 58 51				No orthopnea of necessity
A. P.	62	Arteriosclerotic heart disease, auricular fibrillation	1/ 4/28 1/ 6/28 1/ 9/28 1/13/28 1/18/28 1/22/28 1/25/28 2/ 5/28	20.2 17.7 15.3 15.3 10.9 7.1 7.9 12.0	11.8 18.1 12.3 9.6 11.2 12.6 12.5 9.1	4.225	1.750 1.825 2.025 2.000 2.100 2.000 2.200 1.975	59 57 52 53 50 53 48 53	1.650 1.700 1.925 2.000 1.975 1.825 1.075 1.800	5.7 6.9 4.0 0.0 6.0 8.8 10.2 8.9	-50 +25 -25 -25 +75 +25 -75 -25	
J. D.	65	Arteriosclerotic heart disease, auricular fibrillation	6/27/28 7/ 2/28	7.7 5.2	15.1 12.7	4.200	2.150 2.450	50 43	1.900 2.100	11.6 14.3	+100 +150	

Summary of Observations on Venous Pressure, Vital Capacity of the Lungs, and Degree of Orthopnea—Continued

Sub- ject	Age	Diagnosis	Date	Venous Pressure, Cm. of Water	Occipital Protuber- ance to Right Auricle, Cm.	Vital Capacity					Comment
						Estimated Normal, Cc.	In Orthop- neic Position, Cc.	Reduction from Estimated Normal, per Cent	In Reem- bent Position with Head Flat, Cc.	Decrease from Orthopneic Position, per Cent	Change on Elevating Head, Cc.
M. R.	21	Rheumatic heart disease, mitral stenosis, auricular fibrillation	6/28/28 7/ 3/28 7/ 7/28	20.7 9.6 8.2	13.0 15.0 20.0	3,240	1,750 2,400 2,225	46 35 31	1,475 1,850 2,100	15.7 11.9 5.6	+25 -100 -100
C. W.	57	Arteriosclerotic heart disease, coronary thrombosis	7/ 3/28	16.5	12.0	1,050	..	1,050	0.0	
J. B.	47	Hypertensive heart disease	7/ 3/28	5.8	9.5	2,075	..	1,825	12.0	0
M. B.	36	Rheumatic heart disease, mitral stenosis, auricular fibrillation	7/ 7/28	9.2	19.3	3,200	1,650	48	1,600	3.0	+50
F. M.	46	Rheumatic heart disease, mitral stenosis, auricular fibrillation	7/ 7/28 7/10/28 7/16/28	23.0 21.4 12.0	15.5 22.0 12.5	4,300	1,150 975 1,850	73 78 57	875 900 1,600	23.9 7.7 13.5	+25 +50 +25
M. L.	15	Rheumatic heart disease, mitral stenosis	1/11/29	23.5	15.8	No studies of vital capacity
M. A.	46	Hypertensive heart disease	1/17/29	20.0	13.5	3,140	1,400	55	1,250	10.7	+50
C. B.	41	Rheumatic heart disease, mitral stenosis, auricular fibrillation	1/25/29 1/28/29 1/30/29 2/ 4/29 2/ 7/29	18.2 18.5 20.2 16.7 16.3	13.5 8.5 13.3 8.8 15.8	3,060	1,310 1,490 1,400 1,500	58 62 54 51	1,250 950 1,200 1,475	4.6 20.0 14.3 1.7	+50 +150 +25 0
Average.....						58.4*	8.3*	+14

* Does not include readings taken after disappearance of orthopnea of necessity.

COMMENT

In addition to the evidence presented, we believe that certain clinical phenomena and the following observations of other investigators support the venous pressure theory of orthopnea. Hill¹⁹ stated that any increase in general venous pressure caused a slowing of cerebral blood flow. Wolff and Blumgart²⁵ observed in animals that a definite slowing of the velocity of intracranial blood flow resulted from elevation of the intracranial cerebrospinal fluid pressure. A rise in cerebrospinal fluid pressure is accompanied by an increase in cerebral venous pressure because the skull is a closed cavity without elasticity. The pressures of the cerebrospinal fluid and venous blood must closely approach each other. It therefore may be assumed that Wolff and Blumgart would have observed the same slowing of velocity of blood flow if the cerebral venous pressure had been raised directly instead of indirectly by increasing the intracranial pressure. This work therefore demonstrates the validity of the basic assumption of the venous pressure theory of orthopnea, namely, that an increased general and cerebral venous pressure diminishes the cerebral capillary blood flow.

Salathé²⁶ applied a tambour to the fontanel of an infant 6 weeks old and observed that on his placing the child in a vertical position with the feet down the intracranial pressure fell, and that on his turning the child to a posture with the feet up the pressure rose. Brissaud and Franck²⁷ observed the same changes of pressure in a patient in whom a large portion of the skull had been removed. Hill¹¹ found that the intracranial pressure of a patient who had been trephined was negative while the man sat upright, but became positive as soon as the head was bent down toward the knees or on any expiratory effort. All these observations indicate that in man intracranial pressure and therefore cerebral venous pressure is diminished by changing from the recumbent to the sitting position.

It is well recognized that, in patients with myocardial failure, cyanosis of the face and lips increases in the recumbent position or may appear only in that position. It is probable that this cyanosis is due in large part to retarded capillary blood flow and stagnation anox-

25. Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, *Arch. Neurol. & Psychiat.* **21**:795 (April) 1929.

26. Salathé, A.: Recherches sur le mecanisme de la circulation dans la cavite cephalo-rachidienne, *Trav. du labor. de M. Marey* **2**:345, 1876.

27. Brissaud, E., and Franck, F.: Inscription des mouvements d'expansion et de rétrait du cerveau chez une femme présentant une vaste perte de substance du parietal gauche, *Trav. du labor. de M. Marey* **3**:137, 1877.

emia.²⁸ Since such alterations occur in the superficial capillaries in the recumbent position, it is reasonable to suppose that comparable changes take place simultaneously in the capillaries about the respiratory center. In both locations, the decreased capillary blood flow undoubtedly results from the local increase in venous pressure in the recumbent position. This together with the observed correlation between the height of venous pressure and the degree of orthopnea suggests that in patients with myocardial failure the elevated position provides relief mainly by releasing the respiratory center from the effects of increased venous pressure. The correlation between the height of venous pressure and the degree of orthopnea suggests further that these patients at all times tend to maintain an elevation which is sufficient to keep the respiratory center above the meniscus of the column of venous blood extending upward from the right auricle. In this way, the flow of blood in the capillaries in the region of the respiratory center is kept as efficient as is possible with the existing myocardial failure.

It is a common clinical observation that in patients with congestive failure the jugular veins are engorged as high as the angle of the jaw in the recumbent position, but when the upright posture is assumed the column of blood is visible for only a short distance above the clavicle. Similar changes occur when the head is flexed on the thorax in the recumbent position. This indicates that any elevation of the head reduces the cerebral venous pressure and therefore the venous pressure about the respiratory center. This observation and the relief experienced in the recumbent position when the head is elevated strongly support the venous pressure theory of orthopnea. Of all the theories of orthopnea, only the venous pressure theory and Sahli's¹⁰ hypothesis of the effect of gravity on cerebral venous congestion can explain the relief experienced by the patient on flexing the head on the thorax. As the position of the thorax and abdomen is unchanged when the head is elevated, the increased comfort cannot be due to an alteration in the amount of blood in the lungs. Similarly, the relief cannot be attributed to increased efficiency of the abdominal and thoracic accessory muscles of respiration, to changes in reserve air, middle capacity or vital capacity of the lungs, or to alterations in lung expansion.

It may be contended that according to our hypothesis a normal person should suffer from intense dyspnea due to increased venous pressure when the head is held lower than the rest of the body. The work of Wolff and Blumgart²⁵ indicates, however, that, in such subjects, the increased venous pressure is balanced by either an increased arterial pressure or arteriolar dilatation. In either case, the normal pressure gradient in the capillaries would be maintained. In patients.

28. Lundsgaard, C., and Van Slyke, D. D.: *Cyanosis, Medicine* 2:1, 1923.

with circulatory failure, however, vasodilatation is already present, and an increase in arterial pressure in all probability does not take place. The cyanosis of the face observed in normal persons when the head is held lower than the rest of the body may well be related to the type of cyanosis observed by Goldschmidt and Light²⁹ in which no change in the venous oxygen unsaturation took place.

The evidence which we have accumulated from our own observations and from the investigations of others is in accord with the venous pressure theory of orthopnea. It should be recognized, however, that some of the factors considered as of primary importance by other investigators undoubtedly contribute to the relief experienced in the sitting position. The more complete oxygenation of the blood in the lungs in the upright as compared with the recumbent posture⁸ must aid in securing the relief experienced by the patient in the former position. Furthermore, in those patients who show an important increase in vital capacity of the lungs on changing from the recumbent to the sitting posture,⁷ this increase must be responsible, in part, for the comfort obtained. In patients with ascites,¹⁰ the upright position undoubtedly affords relief partly because this position facilitates diaphragmatic movements. We believe, however, that in all patients with congestive heart failure and increased venous pressure, the relatively low cerebral venous pressure obtained in the sitting position is the primary factor in reducing the respiratory discomfort.

SUMMARY

1. A new theory of the mechanism of orthopnea in uncomplicated myocardial failure of the congestive type is offered. This theory is based on the fact that increased cerebral venous pressure diminishes intracranial blood flow, thereby favoring increased anoxemia of the respiratory center. Accordingly, a patient with myocardial failure and increased venous pressure always tends to maintain an elevation in bed sufficient to keep the respiratory center above the meniscus of the column of venous blood extending upward from the right auricle. In the upright position, the pressure in the veins about the respiratory center is kept more nearly normal than in any other position, and the blood flow in the capillaries feeding these veins is increased to the maximal limit set by the existing myocardial failure.

2. In order to test the validity of the hypothesis, eighty-two comparisons of the height of venous pressure and the degree of orthopnea were made in twenty-two patients with uncomplicated myocardial failure of the congestive type.

29. Goldschmidt, S., and Light, A. B.: A Cyanosis, Unrelated to Oxygen Unsaturation, Produced by Increased Peripheral Venous Pressure, *Am. J. Physiol.* **73**:173, 1925.

3. A parallelism between the two measurements was observed. In general, it was found that the higher the venous pressure, the greater was the orthopnea.

4. When orthopneic patients were placed in the recumbent position with the head flat, simple elevation of the head by flexion of it on the thorax produced, almost without exception, conspicuous diminution of respiratory distress. This procedure favors diminution of the cerebral venous pressure, but has no significant effect on the vital capacity of the lungs. These observations strongly support the venous pressure theory of orthopnea.

5. In striking contrast to the definite correlation between the venous pressure and the degree of orthopnea, no such correlation was observed between the percentage reduction of the vital capacity of the lungs and the degree of orthopnea.

6. The extent of the diminution of the vital capacity of the lungs does not appear to be an important factor in determining the degree of elevation which gives the patient maximum relief.

7. Orthopnea of necessity was observed in patients in whom the vital capacity of the lungs was not significantly increased by changing from the recumbent to the sitting position.

8. Although various factors contribute to the relief experienced in the sitting position, observations indicate that in all patients with congestive heart failure and increased venous pressure, the relatively low cerebral venous pressure in the upright posture is the primary factor in reducing the respiratory discomfort.

THE BLOOD IN LIPOID NEPHROSIS

WITH SPECIAL REFERENCE TO THE ABSENCE OF ANEMIA *

DWIGHT L. WILBUR, M.D.

Fellow in Medicine, the Mayo Foundation

AND

GEORGE E. BROWN, M.D.

ROCHESTER, MINN.

The most striking feature in lipoid nephrosis, aside from the edema, is the patient's pallor, which suggests the presence of considerable anemia. Examination of the blood, however, often shows that the erythrocytes and the hemoglobin are normal. For this reason, statistical data on this point were assembled. It is well known that in another form of renal disease, chronic glomerular nephritis, secondary anemia is frequently a prominent feature; in fact, this has been shown to be of accurate prognostic value.¹

It is generally accepted that pure lipoid nephrosis is a definite clinical entity, although it occurs rarely. It is much more common to observe cases of diffuse nephritis in which the nephrotic or tubular element is predominant. Müller² introduced the term "nephrosis" in 1905 as representing a degenerative renal lesion, in contradistinction to nephritis, in which there is an infectious and usually a glomerular process. However, Aschoff³ and others believed that an inflammatory process is always present in renal disease, and such writers as Löhlein,⁴ Kollert,⁵ and Elwyn⁶ stated that nephrosis begins as acute glomerular nephritis. They agreed that this process may later subside and give

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* From the Division of Medicine, the Mayo Clinic.

1. Brown, G. E., and Roth, Grace M.: Prognostic Value of Anemia in Chronic Glomerular Nephritis, *J. A. M. A.* **81**:1948 (Dec. 8) 1923.

2. Müller, Friedrich: *Morbus Brightii*, *Verhandl. d. deutsch. path. Gesellsch.* **9**:64, 1905.

3. Aschoff, quoted by McElroy, J. B.: *Nephroses*, *J. A. M. A.* **89**:940 (Sept. 17) 1927.

4. Löhlein, M.: *Ueber die Entzündlichen Veränderungen der Glomeruli der Menschlichen Nieren und ihre Bedeutung für die Nephritis*, Leipzig, S. Herzel, 1907, p. 98.

5. Kollert, V.: *Das Problems der Lipoidnephrose*, *Klin. Wchnschr.* **5**:441, 1926.

6. Elwyn, Herman: *The Pathogenesis of Lipoid Nephrosis*, *Arch. Int. Med.* **38**:346 (Sept.) 1926.

way to almost pure nephrosis, but that glomerular inflammatory lesions may always be found on pathologic examination in such cases.

It is also generally conceded that in cases of lipid nephrosis metabolism is profoundly disturbed. This has been especially emphasized by Epstein; the condition is indicated by hypoproteinemia, hyperlipemia and marked generalized edema, which probably is not entirely of renal origin. Chronic diseases, as a rule, are accompanied by anemia which is secondary to the disease process and frequently of significance in the consideration of the patient. In view of the marked pallor, the possibility of previous glomerular involvement, the profound metabolic disturbances and the frequent chronicity of the disease, anemia might possibly be expected in cases of lipid nephrosis.

HISTORICAL DATA

Many statements have been made concerning the blood counts in lipid nephrosis, but these have been substantiated with few figures. Munk,⁷ who expressed the belief that most cases of nephrosis are syphilitic in origin, described the clinical picture as one of marked anemia, edema, oliguria, albuminuria, casts and low blood pressure. Volhard⁸ stated that investigations of his colleague, Keller, have shown that in the early stage of nephrosis, hydremia does not exist, but that, on the contrary, the blood is abnormally concentrated. The erythrocyte count is at the upper limit of normal, and the viscosity may be increased. He expressed the belief that with the onset of diuresis and the disappearance of edema, hydremia develops. The erythrocyte count falls and may decrease to the extent of from 1,000,000 to 2,000,000 in each cubic millimeter; at this point, the anemia becomes apparent for the first time. Linder, Lundsgaard, Van Slyke and Stillman⁹ reported on the blood counts in five cases of subchronic glomerular nephritis of the nephrotic type and on two cases of pure nephrosis. In the latter cases, the erythrocyte count was normal, whereas in the five mixed cases of nephrosis definite anemia was shown. Brown and Rowntree,¹⁰ following a study of nine cases of pure and mixed nephrosis, stated: "Anemia is not marked or constant in nephrosis. Our data show that in five of the nine cases the hemoglobin values and the values obtained by the

7. Munk, Fritz: *Klinische Diagnostik der degenerativen Nierenerkrankungen*, Ztschr. f. klin. Med. **78**:1, 1913.

8. Volhard, Franz: *Die doppelseitigen hämatogenen Nierenkrankungen (Bright'sche Krankheit)*, Berlin, Julius Springer, 1918.

9. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, E.: *Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis*, J. Exper. Med. **39**:921, 1924.

10. Brown, G. E., and Rowntree, L. G.: *Blood Volume in Edema of Glomerular Nephritis and Nephrosis*, Arch. Int. Med. **41**:44 (Jan.) 1928.

hematocrit were normal; in the remaining four cases there was a mild degree of anemia. . . . The mean hemoglobin in grams per cent was 15.7 and the mean percentage of cells as ascertained by the hematocrit was 37.5." In summary they concluded: "In cases of nephrosis with edema, approximately 50 per cent do not show anemia, the remainder show mild grades of anemia." The criteria used in these cases were not so rigid as those employed in our study. Albutt,¹¹ in a clinical lecture on renal dropsy, remarked: ". . . remembering that these patients are always anemic" Kaufmann and Mason¹² remarked: "There is a moderate but progressive anemia in this disease." Concerning nephrosis Epstein¹³ said: "A certain degree of dilution develops which is occasionally more marked in the early than late stages [possibly during the acute glomerular stage according to Elwyn,⁶ Löhlein⁴ and Kollert⁵]. The red blood cells become diminished in numbers and the hemoglobin falls." Altnow¹⁴ cited a case of nephrosis in which the "blood picture remained normal despite a constant loss of albumin in the urine." Boyd¹⁵ mentioned that moderate but progressive anemia is present in nephrosis. Lewis and Scriver¹⁶ stated that the skin takes on an extreme pallor which is out of proportion to the blood count. Elwyn¹⁷ stated that in lipoid nephrosis formed elements of the blood show little change: "Moderate anemia is usually present. The red blood cells are usually around 4,000,000 for each cubic millimeter. The hemoglobin averages from 70 to 80 per cent. With reabsorption of the edema fluid, the blood is temporarily diluted and the anemia seems to increase. There is no change in the leukocytes." Elwyn did not give actual counts nor did he give the number of cases reviewed, or the method used in the determination of hemoglobin.

In the study of fourteen children with lipoid nephrosis, Schwartz and Kohn¹⁸ reported: "The anemia of this disease is usually of a mild

11. Albutt, T. G.: A Clinical Lecture on Renal Dropsy, *Brit. M. J.* **2**:395, 1928.

12. Kaufmann, Joseph, and Mason, Edward: Nephrosis: A Clinical and Pathologic Study, *Arch. Int. Med.* **35**:561 (May) 1925.

13. Epstein, A. A.: Clinical Types of Chronic Parenchymatous Nephritis: Their Treatment and Results, *M. Clin. North America* **4**:145, 1920.

14. Altnow, H. O.: The Evolution of Nephritis; Its Prognosis and Treatment: II. Prognosis in Nephritis, *Minnesota Med.* **10**:231, 1927.

15. Boyd, William: Nephrosis, *Canad. M. A. J.* **16**:349, 1926.

16. Lewis, D. S., and Scriver, W. deM.: The Response of Chronic Nephrosis to Parathyroid and Thyroid Medication, *Ann. Int. Med.* **2**:66 (July) 1928.

17. Elwyn, Herman: Nephritis, New York, The Macmillan Company, 1926, p. 194.

18. Schwartz, Herman, and Kohn, J. L.: Studies of Nephritis in Children: I. Nephrosis, *Am. J. Dis. Child.* **24**:125 (Aug.) 1922.

secondary type and it is only at the end of the disease that the hemoglobin may drop below 50 per cent, the red cells rarely falling below 3,000,000, there not being much difference before, during or after disappearance of the anasarca." From this series of fourteen children they concluded that the children often looked very anemic, but that the absolute anemia was not very great. Davison and Salinger,¹⁹ in a study of twenty-six cases of nephrosis in children, stated: "The hemoglobin content was over 85 per cent (Sahli) in only two patients. The average was 69 per cent with minimal and maximal values of 52 per cent and 95 per cent." In this group were cases in which glomerular lesions were obvious and several in which there was severe infection, so that these values are not conclusive. Marriott²⁰ remarked: "There is a secondary anemia . . . A high protein diet leads to a disappearance of the anemia." In another paper,²¹ he stated: "Secondary anemia rapidly develops. Not only are the red blood cells and the hemoglobin diminished but the serum protein and the blood mass are diminished also." Clausen²² stated that in children with nephrosis, moderate but severe anemia always occurs. He added: "The capillaries of the nail beds show at most the changes due to anemia. . . . Transfusion is indicated for anemia and also has been of benefit in temporarily increasing protein of the blood." It must be remembered that in children with nephrosis, accessory nasal sinus infection²² and pneumococcic peritonitis¹⁰ are often prominent features, and in the presence of active infection the blood count and hemoglobin may be altered by these factors alone.

One would conclude from the foregoing data that the adult with nephrosis is usually pale or pasty in appearance, but that the blood is only slightly, if at all, anemic. In the child, however, the anemia is more marked and may in fact be so progressive as to warrant transfusion of blood.

Material Studied and Criteria for Selection.—In the period from 1921 to 1929 there were registered at the Mayo Clinic twenty-five cases of pure lipoid nephrosis and twenty-six cases of the mixed form in

19. Davison, W. C., and Salinger, Robert: Tubular Nephritis (Nephrosis) in Children and Its Relationship to Other Forms of Nephritis, *Bull. Johns Hopkins Hosp.* **41**:329, 1927.

20. Marriott, W. McKim: Nephritis: Some Newer Viewpoints Concerning Its Nature and Treatment, *Northwest Med.* **24**:472, 1925.

21. Marriott, W. McKim: Newer Knowledge Concerning Nephritis, *Illinois M. J.* **51**:120, 1927.

22. Clausen, S. W.: Parenchymatous Nephritis: I. As a General Systemic Disorder, *Am. J. Dis. Child* **29**:581 (May) 1925; II. Infection of the Paranasal Sinuses as Etiology, *ibid.* **29**:587 (May) 1925.

which the nephrotic element predominated. Epstein,²³ in describing nephrosis, stated: "We have therefore a disease of gradual onset, chronic course, characterized by edema, anasarca and effusion in the serous cavities, by a marked albuminuria with or without casts, and the absence of any blood in the urine, by the absence of hypertension and cardiac hypertrophy; a reduction in the protein content of the blood, inversion of the albumin-globulin ratio and by the increase of the blood, lipoids and finally by a reduction in the basal metabolism." This is the classic picture of so-called chronic lipoid nephrosis which is a rare disease. In selecting the group of pure cases of nephrosis in the present work, we have used the following criteria: (1) edema, graded 2, which has persisted for at least a month; (2) absence of any hematuria except possibly an occasional erythrocyte in the urine; (3) albuminuria, graded 2; (4) systolic blood pressure of less than 140, and diastolic, 90, measured in millimeters of mercury; (5) blood urea of less than 40 mg. for each 100 cc.; (6) phenolsulphonphthalein return of at least 40 per cent in two hours, and (7) normal fundus oculi save for edema or lipemia retinalis. Cases of toxic nephrosis such as are seen in mercuric chloride poisoning have not been included in this study.

In most of the cases, quantitative studies of the proteins and the lipoids in the blood were made, and hypoproteinemia and hyperlipemia were found to be present. In cases in which the albumin-globulin ratio was studied, it was found to be inverted.

The first group of twenty-five cases of pure nephrosis fit in with these criteria; therefore, for the sake of brevity, the actual observations in each case in this group will not be recorded here.

The second group included twenty-six cases of chronic diffuse nephritis of the nephrotic type. They were separated from the first group because in various ways they did not satisfy the criteria for pure nephrosis, but at the same time they displayed clinical pictures which were definitely nephrotic.²⁴

The methods of determining the hemoglobin in these cases were as follows:

1. The Dare method, which is reported in percentages of hemoglobin. Chart 1 shows the relationship between the readings of hemoglobin by the Dare and the Palmer-Haldane methods. This figure shows that a reading of 70 per cent, or above, by the Dare method, is a normal value for hemoglobin, and 70 per cent has been taken as the lower limit of normal in the present work.

23. Epstein, A. A.: *Clinical Course and Therapeutic Management of Chronic Nephrosis*, M. Clin. North America 5:1067, 1922.

24. After careful observation, diagnosis of these cases was made by Dr. N. M. Keith and Dr. E. G. Bannick.

2. In many of the cases, the more accurate method of Osgood and Haskins²⁵ has been used. The normal value for the acid hematin by this method has been shown by Osgood²⁶ to be 15.76 Gm. for each 100 cc. of blood, in the male. Haden,²⁷ using the oxygen capacity of the blood as a measure of the hemoglobin content, found it to average 15.6 Gm. in each 100 cc. of blood in normal persons of both sexes. An erythrocyte count of 4,000,000, or more, has been taken as normal.

RESULTS

The results of the study of the blood count in the two groups of cases have been summarized. In the twenty-five cases of pure nephrosis, the mean erythrocyte count with the probable error was $4,350,000 \pm 50,000$, with extremes of 3,310,000 and 5,490,000 for each cubic millimeter in a total of ninety-eight counts. The mean value for hemoglobin for the same group was 75.4 per cent (Dare), which again is well above the normal limits. The extreme variations in this group were 62 and 95 per cent. The much more accurate acid hematin method of Osgood and Haskins in twenty-one of these cases in which it was done showed a mean value of 15.55 Gm. in each 100 cc., which corresponds well with the normal accepted value of 15.76 Gm. in each 100 cc. Of these twenty-five cases of pure nephrosis, one case only showed definite anemia with both the Dare and the Osgood-Haskins determinations for hemoglobin. The remainder of the cases showed a normal value by one or both methods. The leukocyte count was normal in almost every instance. In occasional cases, unexplained moderate leukocytosis was present.

In the second group, comprising twenty-six cases of chronic nephritis of the nephrotic type, the mean erythrocyte count with the probable error was $3,845,000 \pm 63,000$, with extremes of 2,150,000 and 5,100,000 for each cubic millimeter. The mean hemoglobin value was 66.67 per cent (Dare) with extremes of 38 and 89 per cent, and the mean value for the acid hematin in nineteen of the twenty-six cases was 13.3 Gm. for each 100 cc. Nineteen (73 per cent) of the patients showed definite evidence of anemia. The leukocyte count was perhaps slightly higher in this group than in the first group, which probably can be explained by the fact that acute and chronic infection was much more frequently found in the mixed than in the pure types of nephrosis. The contrast in the results of the two groups may be noted in chart 2.

25. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57**:107, 1923.

26. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index, and Volume Index Standards, *Arch. Int. Med.* **37**:685 (May) 1926.

27. Haden, R. L.: Accurate Criteria for Differentiating Anemias, *Arch. Int. Med.* **31**:766 (May) 1923.

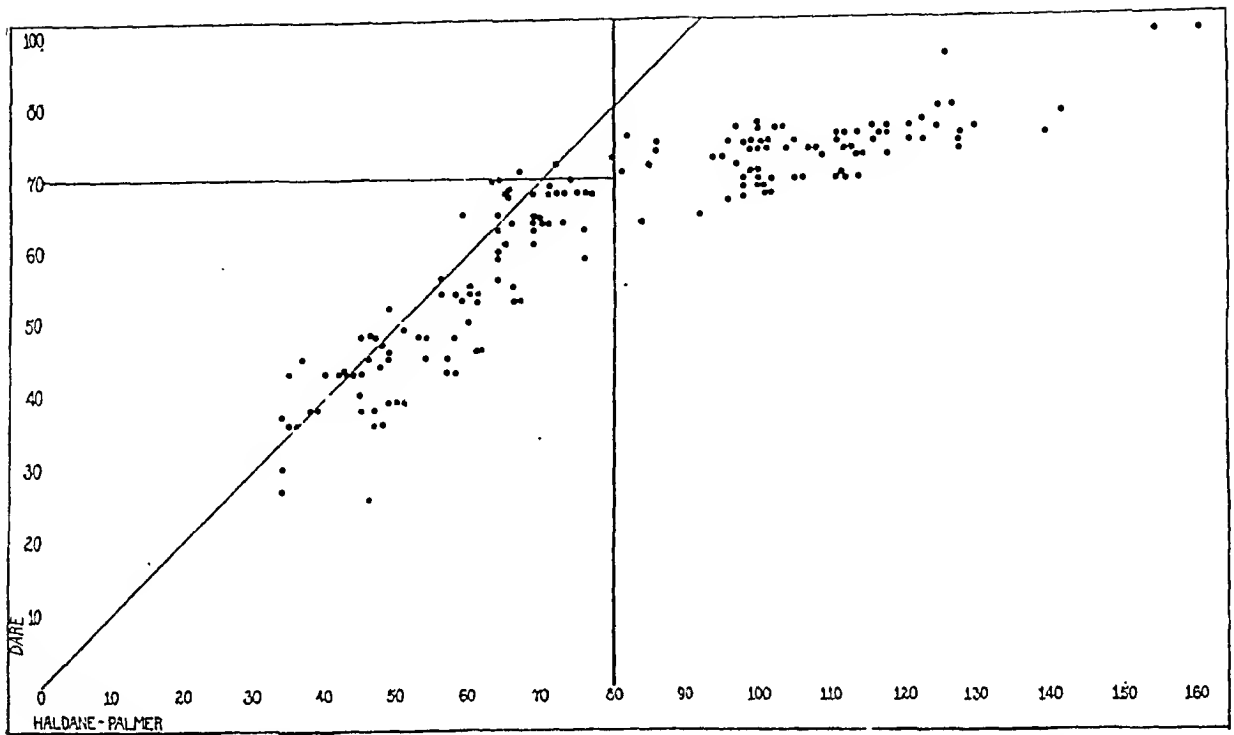


Chart 1.—Relationship of Dare and Haldane-Palmer estimations of hemoglobin.

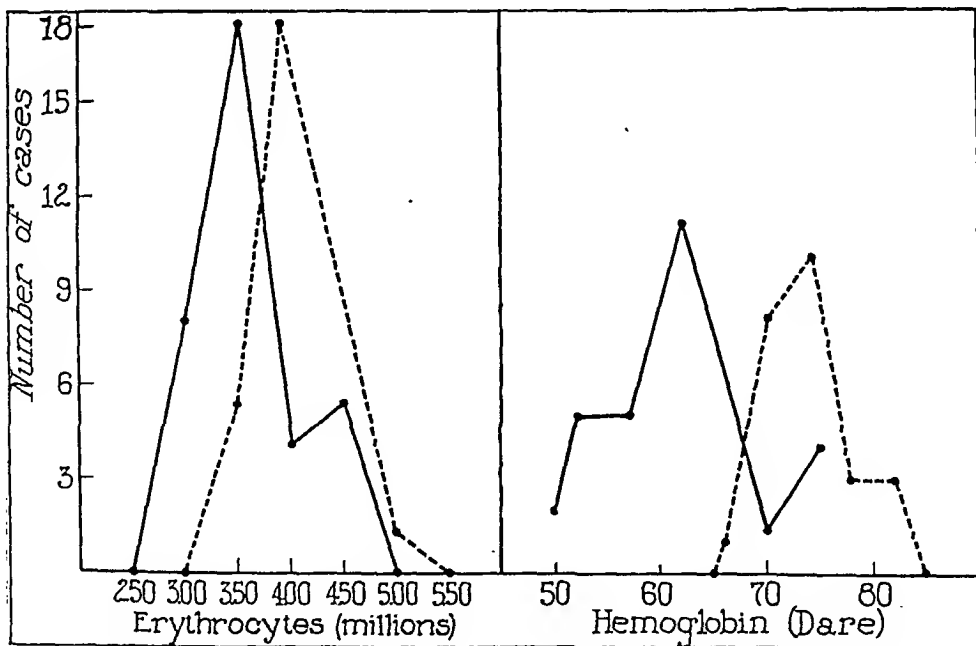


Chart 2.—Comparison of erythrocytes and hemoglobin in mixed nephrosis and pure nephrosis; the dash line indicates mixed nephrosis; the dotted line, pure nephrosis.

BLOOD VOLUME

The effect of edema and diuresis on the blood volume in renal disease has been widely discussed. The presence of marked edema and the frequent occurrence of anemia in nephritis have led certain observers to conclude that hydremia or edema of the blood is associated with dilution anemia. Fluctuations in the concentration of the plasma protein or other constituents of the blood during the course of the disease have been used as a measure of the amount of dilution of blood. Linder, Lundsgaard, and Van Slyke²⁸ and others have shown that variations in the concentration of the plasma protein are due to absolute variations in this substance and not to variations in the blood volume and plasma volume.

In three cases in each of the two groups the blood volume was studied by the dye method of Keith, Rowntree and Geraghty.²⁹ It was realized, as Bennhold³⁰ pointed out, that congo red, which it used in this determination, disappears rapidly from the circulation in cases of pure nephrosis because of elimination through the kidney. Brown and Rowntree have shown, however, that the rate of disappearance of the dye in pure nephrosis averages only 1.5 per cent more than the normal within the three, four and six minute intervals following injection. This is well within the limits of error and indicates that such determinations are probably fairly accurate in this disease during this short interval.

The blood volume in the six cases has been calculated on the basis of the body weight during the period of edema and in the edema-free state, which are designated, respectively, as the uncorrected and the corrected body weight. The surface area has been calculated according to the DuBois standards, the corrected body weight only being used. In the three cases of pure nephrosis, the blood volume according to the uncorrected body weight was less than the normal mean of 89.1 cc. for each kilogram.¹⁰ On the basis of corrected body weight, however, the values are all above this normal mean value, but are close enough to this mean to constitute normal values. The volume of plasma for each kilogram of body weight was normal in one case, and considerably increased in the other two. In one of the three cases, at the time of examination, definite, although slight, anemia was present, whereas in the other two, the values for hemoglobin were normal. At the same time, this anemic

28. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, *J. Exper. Med.* **39**:887, 1924.

29. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**:547 (Oct.) 1915.

30. Bennhold, H.: Ueber die Absorptionsfähigkeit der Serumkolloide tubulär Nierenkranker gegenüber Farbstoffen, *Ztschr. f. d. ges. exper. Med.* **49**:71, 1926.

patient showed an increased percentage of plasma in the plasma-cell relationship as shown by the hematocrit.

In two of three cases of mixed nephrosis, the blood volume for each kilogram of corrected body weight was distinctly elevated. In one of these, the elevation was representative of relative and absolute increase in the plasma volume, and in the other it was the result of an absolute increase in the total volume of the blood, the cell-plasma relationship remaining approximately normal. In both of these cases there was considerable anemia at the time of the examination, as shown by the acid hematin values of 11.1 and 11.9 Gm. for each 100 cc. The remaining case showed only moderate diminution in volume and a normal value for hemoglobin.

In three cases, blood volume studies were made before and after diuresis had occurred.

TRANSITION OF NEPHROSIS INTO GLOMERULAR NEPHRITIS (ILLUSTRATIVE CASE)³¹

The patient in this case fulfilled all the criteria for the diagnosis of pure chronic lipoid nephrosis. Within a short time, chronic glomerular nephritis developed, and the outcome was fatal. From the standpoint of the blood count alone, the development in this case was dramatic and showed the close relationship between anemia and glomerular disease.

A man, aged 32, presented himself at the Mayo Clinic on May 16, 1926, with a history of four months of general anasarca of undetermined origin. A diagnosis of pure nephrosis was made (table 1). Edema of the lower extremities, graded 2, ascites, graded 2, and slight hydrothorax were present. The urine contained albumin, graded 2, and many casts, but erythrocytes were not found at any time. The systolic blood pressure was 120, and the diastolic, 90, measured in millimeters of mercury. The basal metabolic rate was -12 , the blood urea was 37 mg. for each 100 cc., the phenolsulphonphthalein return in two hours was 60 per cent, the plasma protein 4.06 Gm. for each 100 cc., and the cholesterol of the blood was 344 mg. for each 100 cc. The erythrocytes numbered 4,500,000; the hemoglobin was 70 per cent (Dare) and 17.5 Gm. for each 100 cc. (Osgood and Haskins). The patient lost weight, decreasing from 158 pounds on entrance to 113 pounds on dismissal, largely owing to disappearance of the edema following treatment with a diet low in salt and in protein and intensive treatment by ammonium chloride and merbaphen. The blood count on dismissal was about the same as on admission, and the patient appeared to be in good condition.

The patient returned in October, 1926, for reexamination. At this time, nine months after the onset, the blood pressure was slightly elevated (158 systolic and 115 diastolic), and there was early evidence of renal insufficiency, with an output of phenolsulphonphthalein of 30 per cent in two hours, blood urea 52 mg. for

31. This case resembles a case reported by E. H. Mason (*The Life History of a Case of Nephrosis*, *Internat. Clin.* 50:163, 1926) and one reported by Brown and Rowntree.

each 100 cc. and creatinine of 3.2 mg. for each 100 cc. The results of the examination of the fundus oculi were still negative. The erythrocytes numbered 3,100,000, and the hemoglobin was 68 per cent (Dare). The patient felt reasonably well. There was, however, definite evidence of glomerular involvement.

Five months later, the patient returned again because of headaches, blurred vision, vomiting and loss of weight. He was obviously in poor condition and was anemic. He was placed in the hospital, where marked renal impairment was noted. The blood urea was 221 mg. for each 100 cc., the systolic blood pressure was 210 and the diastolic 140; the phenolsulphonphthalein return was 5 per cent. Ophthalmic examination showed anemic disks with mild edema of the retina surrounding them and extending to the macular regions. There were a few small hemorrhages, and the examiner concluded that the change indicated early first stage of glomerular nephritis. The erythrocytes numbered 2,250,000, and the hemoglobin was 48 per cent (Dare), evidence of marked secondary anemia. Four days after admission, the patient died. Necropsy showed chronic diffuse nephritis.

TABLE 1.—*Transition from Pure Nephrosis to Glomerular Nephritis: Effect on Blood Count*

Date	Weight, Kg.	Edema, Grade	Blood Pressure		Basal Metabolic Rate	Erythrocytes, Millions	Hemoglobin		Blood Urea, Mg. for Each 100 Ce.	Blood Creatinine, Mg. for each 100 cc.	Return of Phenol-sulphonphthalein, Per Cent	Erythrocytes in Urine	Blood Cholesterol, Mg. for Each 100 Ce.	Plasma Protein, Gm. for Each 100 Ce.
			Systolic	Diastolic			Per Cent (Dare)	Gm. for Each 100 Ce. (Osgood and Hastings)						
5/16/26*	72.2	Legs, 2 Ascites, 2	120	90	—12	4.28	70	17.5	37	1.4	60	None	284	4.06
6/17/26	51.3	None	118	70	—19	4.57	74	16.2	15	None	344	4.8
10/18/26†	61.6	Ankles, 1	158	115	3.10	68	52	3.7	30	None	327
3/ 4/27‡	61.8	Face, 2 to 3	210	140	2.25	48	221	11.0	5	Many	311	5.8

* Fundus oculi not examined; diagnosis, pure nephrosis.

† Fundus oculi normal; diagnosis, mixed nephrosis.

‡ Blurred vision, headaches, vomiting; first stage retinitis of glomerular nephritis; chronic diffuse nephritis diagnosed. Chronic diffuse nephritis was found at necropsy.

COMMENT

Although glomerular involvement in nephritis is not always associated with anemia, it has been shown that if renal insufficiency supervenes, anemia almost always develops. One would expect, therefore, to find anemia absent in cases of nephrosis without glomerular involvement; that is, in cases of pure nephrosis. That such is actually the case is illustrated by the present study of twenty-five cases of pure nephrosis, in only one of which there was anemia. A follow-up study of this patient revealed that within six months after his blood was last studied at the clinic, definite signs of glomerular nephritis had developed. The cases of mixed nephrosis stand in distinct contrast to those of pure nephrosis. Of the twenty-six mixed cases, nineteen (73 per cent) showed evidence of definite anemia, two thirds of which presented evidence of renal insufficiency; all but one of the remaining third showed mean values for hemoglobin that were approximately the

average in the cases of mixed nephrosis (66.67 per cent Dare), as shown in table 2. These figures show that glomerular involvement as it occurs in cases of mixed nephrosis is usually accompanied by slight anemia. With the development of renal insufficiency, anemia is definite.

In a study of 185 cases of chronic glomerular nephritis in 1922, Brown and Roth³² divided the cases into two groups, those in which anemia was present and those in which it was not present. In the 105 cases in which anemia was present, the average erythrocyte count was 3,310,000 and the average value for hemoglobin was 56 per cent

TABLE 2.—*Analysis of Anemia in Cases of Mixed Nephrosis*

Case	Renal In- sufficiency, Grade	Erythrocytes, Millions (Mean)	Hemoglobin, per Cent (Dare)
1	..	3.88	66
2	..	3.90	68
3	..	3.55	66
4	..	3.15	66
5	..	3.25	55
6	..	3.88	66
7*	1	3.40	54
8	1	4.27	62
9*	3	4.58	66
10*	3	3.60	69
11*	2	3.22	59
12*	1	3.29	57
13*	1	3.59	64
14	1	3.32	55
15*	2	3.68	65
16*	2	4.49	64
17*	1	3.86	62
18	1	3.56	67
19	1	3.40	54
Average for group.....		3.85	66.67

* Patient died.

(Dare). In the absence of anemia (seventy-nine cases), the average erythrocyte count was 4,200,000 and the average value for hemoglobin was 75 per cent (Dare). In 57 per cent of these cases anemia was definite. In a review of the last forty cases of subacute and chronic glomerulonephritis registered at the Mayo Clinic prior to April 1, 1929, distinct anemia was found in twenty-two (55 per cent) as shown in figure 3. The presence of anemia in glomerulonephritis in the absence of complicating disease or infection is probably evidence of existing or preexisting renal insufficiency and therefore has prognostic value. The absence of anemia in certain cases may be an expression of mild glomerular injury not sufficient to produce renal inadequacy. Further work needs to be done on the clarification of this point.

32. Brown, G. E., and Roth, Grace M.: The Anemia of Chronic Nephritis, Arch. Int. Med. 30:817 (Dec.) 1922.

Eleven of the twenty-six patients with mixed nephrosis and only three of those with pure nephrosis are dead. Nine of the eleven patients in the first group were anemic, and most of the deaths were the result of uremia. In the second group, one patient died apparently of uremia; one died of unknown cause shortly after arriving home; the third patient also died of an unknown cause. The study of these cases impresses one with the prognostic value of anemia in cases of mixed nephrosis.

The illustrative case reported herein is an example of pure nephrosis without anemia, and it shows clearly the development of anemia coincident with signs of onset of glomerular disease. It is a strong point in favor of the view that severe glomerular involvement and anemia go hand in hand.

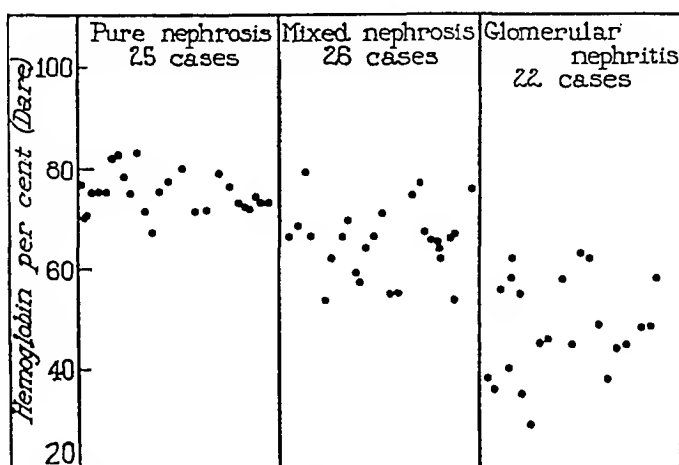


Chart 3.—Incidence of anemia in pure nephrosis, mixed nephrosis and glomerular nephritis.

The studies were made over periods of months to years, and a sufficient number of blood counts was made to give accurate data. In the cases of pure nephrosis, seven of the twenty-five had presented symptoms of the disease for more than five years and yet disclosed blood values that were normal. The fact that the long duration of the disease and therefore its chronicity in some cases show so little effect on the blood count would lead one to believe that the hematopoietic tissues are not affected by the disease process in pure nephrosis.

The results obtained in the present study are not at great variance with those reported in the literature. It was possible to study only two children in the present series, and so the data cannot be compared with those of other workers who have found considerable anemia in children. It would seem logical to believe that nephrosis would affect the blood of children and adults in the same way, and the only explanations for

the discrepancy in the observations in the reported cases of anemia in children with nephrosis and the absence of anemia in such cases in the present study are: (1) failure of the reported cases to fulfil our criteria for pure nephrosis and therefore the inclusion of mixed cases which may show anemia, and (2) the presence of active infection, that is, of nasal sinus and pneumococcic peritoneal inflammation, in so many of the children with nephrosis.³³

The studies of the blood volume in pure nephrosis bring out several points: 1. Neither in the stage of edema nor following diuresis is the blood volume increased to a degree to produce dilution phenomena, nor is it decreased to mask anemia, as suggested by Volhard. 2. In mixed nephrosis there may be moderate increase in the volume of plasma and of blood, especially in the presence of anemia, which is probably due to replacement processes incident to diminished erythrocytes and not to edema or diuresis.

In a larger but less rigidly selected group of cases studied by Brown and Rowntree, it was concluded that 50 per cent of cases of nephrosis (pure and mixed) with edema do not show anemia, and in this group strictly normal values for the volume of blood and of plasma are obtained. In the cases that showed slight grades of anemia, the volume of the blood and of plasma was somewhat higher than the mean value for normal persons. In other respects, also, the results recorded here coincide with those of these workers and are therefore reproduced in tabulation form only.

SUMMARY

In only one of twenty-five carefully selected cases of pure nephrosis did the erythrocyte and hemoglobin values show anemia. The leukocyte and differential counts were normal.

In a similar series of twenty-six cases of mixed nephritis of the nephrotic type, the erythrocytes and hemoglobin values showed anemia in nineteen (73 per cent).

In glomerular nephritis and mixed nephrosis, anemia is common, especially in the presence of renal insufficiency; it is of definite prognostic value.

Cases of nephrosis in which signs and symptoms of glomerular nephritis develop show a gradually developing anemia.

The volume of blood in cases of nephrosis, according to corrected body weight, is slightly above the mean value for normal persons.

The presence or absence of anemia in doubtful cases of renal disease with edema is probably of some diagnostic, and of definite prognostic, value.

33. Davison and Salinger (footnote 19). Clausen (footnote 22).

PULMONARY ATELECTASIS AS A COMPLICATION OF BRONCHIAL ASTHMA *

J. A. CLARKE, JR., M.D.

PHILADELPHIA

Pulmonary atelectasis occurs in two forms, microscopic and macroscopic. The microscopic form has attracted almost no attention so far. It is described in three reports on autopsies in cases of asthma and undoubtedly deserves much more careful study.¹

The macroscopic form was described early in the nineteenth century. Laennec,² discussing a typical case from the practice of Andral,³ considered it a purely nervous form of asthma. The case is similar in symptomatology and gross pathology to the cases now being recognized as massive collapse.

At about the same time, English surgeons were studying the condition in children as congenital failure of the lung to expand. Following its experimental reproduction by plugging a bronchus in 1845,⁴ the condition was forgotten clinically until the works of Pasteur⁵ in 1910 to 1914 called attention to its occurrence after operation. This excellent work failed to receive any attention in America until the observations of Scrimger⁶ in 1921 and Leopold⁷ in 1924, since which time it has been freely discussed by surgeons and roentgenologists. Atelectasis was also used by Jackson, Spencer and Manges⁸ since 1920 as an aid in the localization of nonopaque foreign bodies in the lungs.

Atelectasis occurs either as a result of pressure on a normal lung, as in hydrothorax and pneumothorax, or as a result of obstruction of a bronchus by tumors or foreign bodies. It can be produced experimentally by obstructing a bronchus. Its occurrence as a postoperative compli-

* Submitted for publication, Sept. 4, 1929.

* From the Asthma Clinic of Jefferson Hospital.

* Read before the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., June 5, 1929.

1. Huber, H. L., and Koessler, K. K.: Pathology of Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922. Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma: Report of Three Cases, Arch. Path. **5**:1003 (June) 1928. Steinberg, B., and Fegley, K. D.: J. Lab. & Clin. Med. **13**:921, 1928.

2. Laennec: Traite de l'auscultation mediate, ed. 2, Paris, 1826, vol. 2, p. 87.

3. Andral: Clinique Medicale, ed. 2, Paris, 1829, vol. 1, p. 250.

4. Mendelssohn, A.: Der Mechanismus der Respiration und Cirkulation, Berlin, B. Behrs, 1845, p. 177.

5. Pasteur: Lancet **2**:1080, 1910.

6. Scrimger: Surg. Gynec. Obst. **32**:486, 1921.

7. Leopold: Am. J. M. Sc. **167**:421, 1924.

8. Jackson, Spencer and Manges: Am. J. Roentgenol. **7**:277, 1920.

cation was proved, in a large number of cases, to be due to a plug of tenacious mucus in a large bronchus.

In typical bronchial asthma the occurrence of massive collapse was reported three times, once by Berkhard⁹ in 1889, once by Kamchorn and Ellis¹⁰ in 1921 and once by Sante¹¹ in 1928. In Andral and Laennec's case the symptoms, signs and observations at autopsy point strongly to atelectasis. The man had had a chronic cough for years, but had not had dyspnea until a few hours before death. Laennec, however, considered the attack asthma.

The case of Berkhard and that of Kamchorn and Ellis undoubtedly occurred in persons who had been asthmatic for many years. Both, however, were complicated by cardiac failure. These observers believed that their patients died in asthmatic paroxysms.

There are few notes on Sante's case, but there can be no doubt but that the child had asthma. This case was complicated by the presence of pneumothorax on the same side as the atelectasis, but the atelectasis was not caused by the pneumothorax. After examining the roentgenograms of Sante, one is easily convinced of the accuracy of his interpretation, paradoxical as it may seem at first. The child made a complete recovery from both conditions. There was no previous operative work in any of the three cases.

In addition to these three cases, two additional cases are here reported; in one the condition was diagnosed by routine roentgen examination and in the other at autopsy. Both patients showed the same symptoms as in the postoperative cases. One patient recovered completely, as is shown by the roentgenograms.

REPORT OF CASES

CASE 1.—J. W., a white woman, aged 32, married, came to the asthma clinic on July 12, 1928. Her paternal grandfather had had asthma after he was 80. Soon after an attack of "typhoid-pneumonia" at 5 years of age, she developed asthma, which continued at intervals, becoming worse during the last few years before examination.

Physical examination showed an emaciated young woman with a large, flat chest. The wheezing râles of asthma were heard all over both lungs. The heart showed a split first sound and a systolic murmur at the apex. Roentgen examination showed adhesions of the right diaphragm. The heart was small and normally placed, and both lower lobes were normally distended with air. The nasal septum was deflected, but no definite disease of the accessory sinuses was diagnosed by either rhinologist or roentgenologist. The teeth were in poor condition, and four abscesses were found at their roots. There were no positive skin reactions.

9. Berkhard: *Asthma*, ed. 2, London, 1889, p. 73.

10. Kamchorn and Ellis: *Am. J. M. Sc.* **161**:525, 1921.

11. Sante: *Am. J. Roentgenol.* **20**:213, 1928.

On July 27, she was seized with such a severe paroxysm of dyspnea that her private physician, Dr. Bender, thought she was dying. She was admitted to the ward on the following day. Another roentgenogram was taken on August 1 and showed the right lower lobe collapsed, with the heart and trachea displaced to the right side. A third picture, taken on August 9, showed the lung still collapsed, but the displacement of the heart was not so great. On August 10, bronchoscopy was done by Dr. Clerf, but no obstruction was found.

A final picture, taken on September 13, showed the previously collapsed lobe completely expanded.

She had an irregular fever (the highest temperature recorded being 102.6 F.) for the first four days of her stay in the hospital. The highest respiratory rate

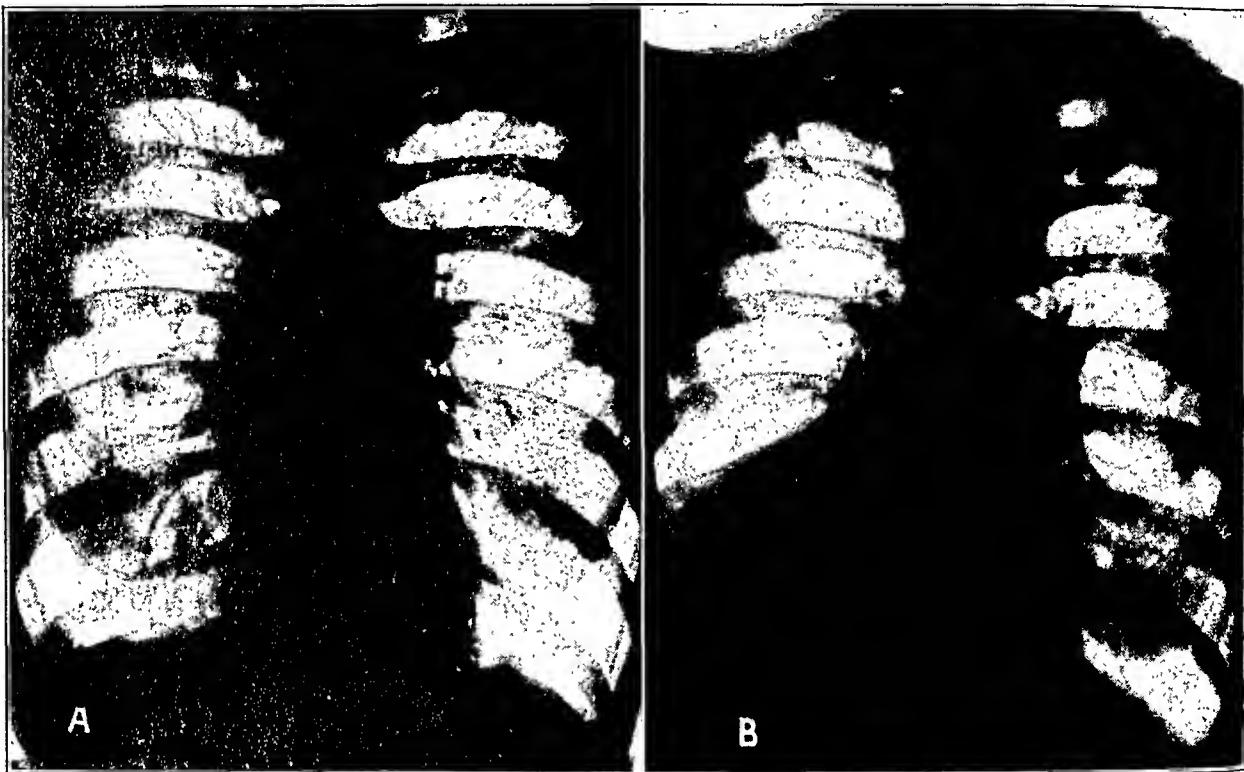


Fig. 1 (case 1).—*A*, lungs two weeks before atelectasis, showing diaphragmatic adhesions and expansion of right lower lobe; *B*, three days after onset of atelectasis.

was 36 per minute. The asthma decreased in severity rapidly, but was never completely relieved.

CASE 2.—M. K., a white woman, aged 53, unmarried, was admitted to the ward on July 25, 1928. She had asthma for twelve years previous to admission, but was able to work as a domestic servant for most of that time. The asthma was worse following "congestion of the lungs" two years before admission. At the time of admission, she was continuously in a dyspneic condition, except when relieved by doses of epinephrine.

Physical examination showed typical wheezing râles of asthma. A roentgenogram taken on July 28 showed a marked increase in the root shadows and the peribronchial markings. There was air in both lower lobes. The laboratory reported a faint trace of albumin with a few granular casts in the urine. The temperature did not rise above 99.5 F. There were positive skin reactions to grass

pollen, orris root, horse and cat dander. Examination of the nasal sinuses showed no disease. The teeth had all been removed.

On August 1, at 12:30 a. m., the patient said that she was weak and had a headache. Since she had had eight doses of epinephrine during the previous twenty-four hours, she was given $\frac{1}{4}$ grain (0.016 Gm.) of morphine, after which she slept. At 5:15 a. m., it was noticed that she was dyspneic and cyanotic and was unconscious. The heart was beating regularly 120 beats per minute. She was given artificial respiration with 10 per cent carbon dioxide and oxygen, strychnine, atropine, alpha lobeline, caffeine and epinephrine. She became weaker, and died at 6 p. m. without regaining consciousness.

Necropsy was performed by Dr. Bucher. The pericardial space was prominent. The thymus extended to the upper border of the heart; the right side of

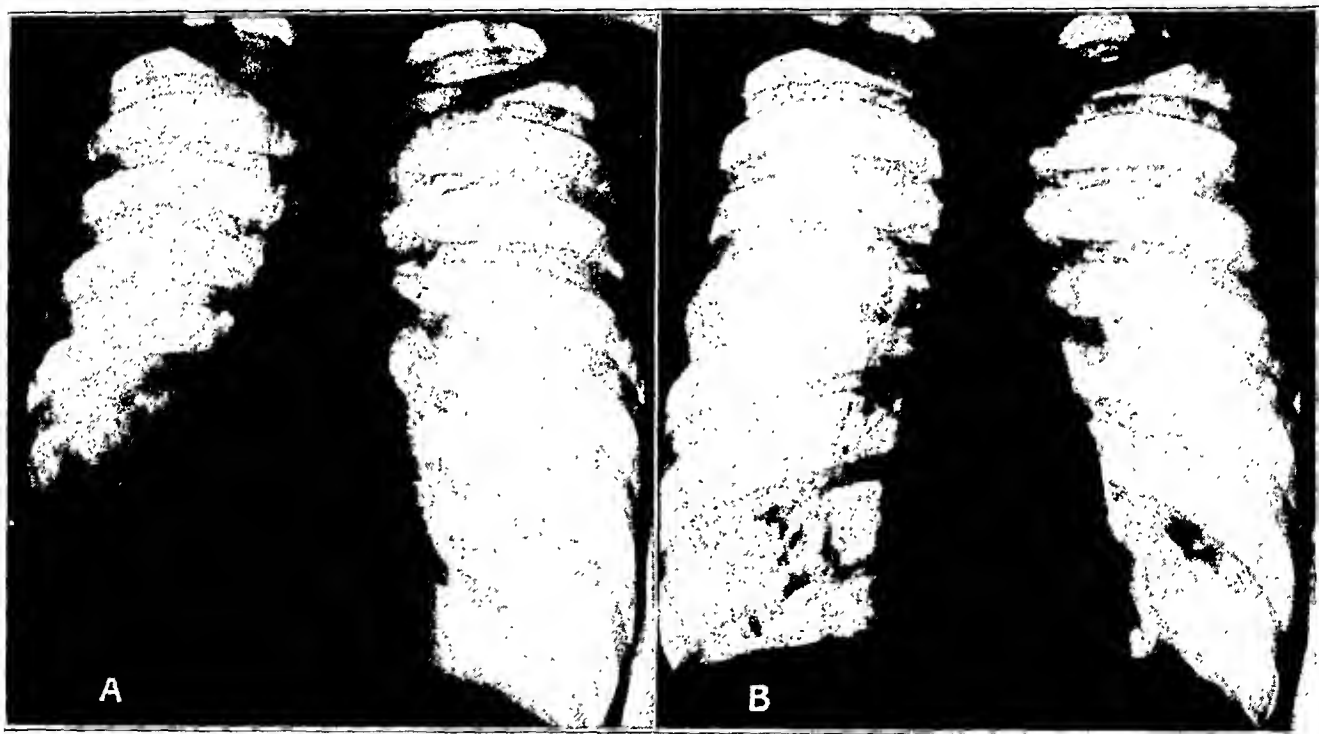


Fig. 2 (case 1).—*A*, lungs eleven days after onset of atelectasis; *B*, six weeks after onset of atelectasis, showing return to normal.

the heart was dilated. The upper lobes of the lungs were voluminous; the lower lobes were flabby and airless.

The tracheal mucous membrane was red and swollen, and the smaller bronchi were filled with yellowish, tenacious mucus. There was a mass of lymph nodes at the junction of the trachea with the left main bronchus. There were many distended air vesicles on the surface of the lungs.

On section, the upper lobes were emphysematous and the lower lobes were red and soggy. On histologic examination, focal atelectasis and bronchial obstruction by mucus were found.

The heart weighed 330 Gm. and had two papillary muscles. The myocardium was grayish red and somewhat flabby. There were a few petechial hemorrhages on the epicardium. Considerable thymic tissue was found in the fibrotic thymus. The liver was normal. The spleen was small but contained a number of small

miliary, grayish-white, calcified nodules. The kidneys and gastro-intestinal tract were normal. There were a few myomas in the small uterus.

A careful study of the reported cases of postoperative atelectasis reveals a percentage of allergic manifestations far higher than that of the general population. Scott¹² reported forty cases in 1925, four of his own and thirty-six from the literature. In spite of the fact that no family histories were given and that the past medical histories were meager, one finds that in five patients there were unmistakable manifestations of allergy before operation. Three patients had had

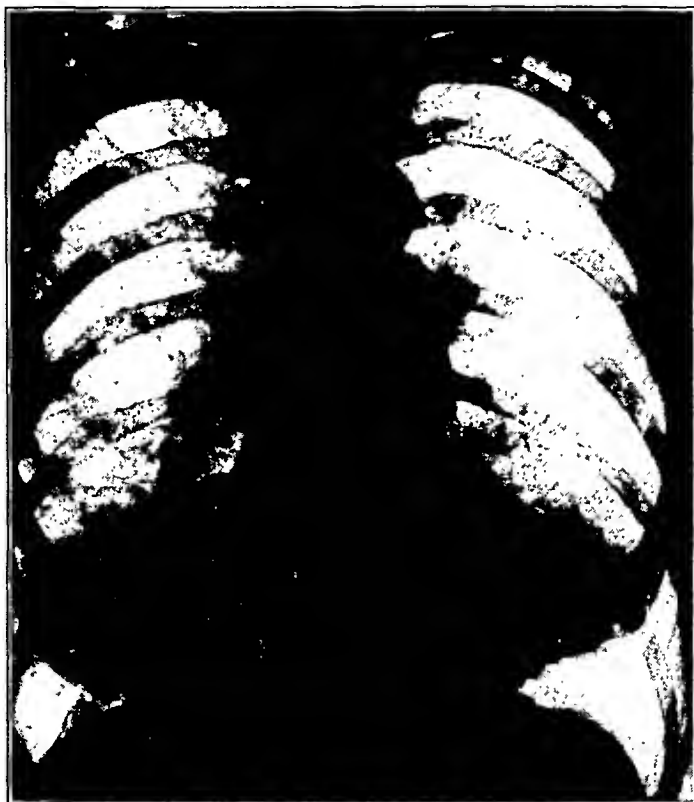


Fig. 3 (case 2).—Lungs four days before atelectasis and death, showing normal aeration of both lower lobes.

asthma and one urticaria, and one had been operated on for angio-neurotic edema of the intestines. Two other patients had had an undiagnosed chronic cough. One had an acute edema of the glottis of the "angioneurotic type" after the operation. Bowen¹³ reported seven cases, in one of which the patient had been asthmatic before operation.

12. Scott, W. J. M.: Postoperative Massive Collapse of Lung, *Arch. Surg.* 10:73 (Jan.) 1925.

13. Bowen: *Am. J. Roentgenol.* 21:101, 1929.

Thus one sees that without the observers' attention being especially directed to allergy, they reported frank allergic manifestations in more than 10 per cent of the cases.

The occurrence of râles in both lungs before the onset of atelectatic symptoms was frequently noted. Elliott and Dingley¹⁴ insisted that bronchitis always preceded the collapse. Ball¹⁵ considered and discarded the theory of the asthmatic nature of the condition, because atelectasis is not a complication of asthma.

Because of the high incidence of allergy in persons with post-operative atelectasis, and the occurrence of atelectasis in persons with asthma on whom surgical procedures have not been carried out, it is suggested that there is an allergic factor in postoperative atelectasis. This may be the bronchitis which is responsible for the tenacious mucus which, in turn, was shown to produce the obstruction in many instances.

Clinically, surgeons recognize two types of atelectasis. In the fulminating type, the onset is sudden, with extreme dyspnea, sense of oppression and cyanosis, and in patients with the more severe cases, with coma and death. As Lee aptly put it: "The patient suddenly presents symptoms of a catastrophe." All of the five patients suffering from asthma exhibited these symptoms. In this type, the symptoms are not explained by either the necropsy or the roentgen observations. The other type is spoken of as a latent type. Here the symptoms are only those of mild respiratory infection, and the dyspnea is only that which is to be expected when a certain amount of lung tissue fails to function.

The explanation of the difference in the two types by the time required to produce the collapse is untenable, because it was shown experimentally that partial obstruction produces obstructive emphysema, and that collapse cannot start until the obstruction is complete. The rate of absorption of the captured air by the blood is probably determined by chemical laws and is not subject to variations.

The suggestion is made here that the fulminating symptomatology of atelectasis is an allergic reaction to the bronchial secretion captured in the collapsed lung and absorbed along with the air, similar to that which one is accustomed to call bronchial asthma. The absence of the typical asthmatic râles over the noncollapsed lobes of the lungs is one point distinguishing this from the ordinary less severe paroxysms of asthma.

14. Elliott and Dingley: *Lancet* 1:1305, 1914.

15. Ball, R. P.: *Pulmonary Atelectasis Following Thyroidectomy: Report of Four Cases with Observations at Necropsy*, *Arch. Path.* 5:763 (May) 1928; *Bilateral Lobar Atelectasis: Report of Case with Autopsy Observations*, *Arch. Surg.* 17:82 (July) 1928.

Small areas of collapsed alveoli were found at necropsy a number of times in persons who had asthma. It seems possible that lobar collapse might result from the coalescing of a number of such areas until the whole lobe would be involved without any obstruction in the larger bronchi. Ball was unable to find any obstruction in the bronchi in four patients, all of whom had lobar collapse.

In the course of asthma, the occurrence of small areas of collapse giving rise to severe paroxysms of dyspnea, which, however, do not prove fatal, is probably fairly frequent. Suggestive roentgen shadows appear and disappear, and on physical examination of the patient scattered areas of diminished breath sounds and moist râles make their appearance from time to time. Acute obstructive emphysema should not be forgotten when such areas are found.

SUMMARY

Lobar atelectasis of the lungs (massive collapse) occurs in persons with bronchial asthma independent of operative procedure and is frequently fatal.

In postoperative atelectasis, previous symptoms of allergy are not uncommon.

The fulminating symptoms are suggestive of an allergic reaction to the captured bronchial secretion.

Small areas of pulmonary atelectasis are probably not uncommon in persons with true bronchial asthma and may explain some of the severe paroxysms.

TETRALOGY OF FALLOT

CLINICAL REPORT OF A CASE *

L. MINOR BLACKFORD, M.D.

ATLANTA, GA.

White and Sprague¹ have recently reproduced extracts from Fallot's original monograph (1888), some of which may be appropriately repeated:

Of these cardiac malformations there is one which in frequency surpasses all others, since we have noted it in almost 74 per cent. of our observations. It is this malformation, then, that the clinician will be justified in diagnosing, and in so doing the chances of error which he will run will be relatively few.

This malformation constitutes a true pathologic-anatomic type represented by the following tetralogy: (1) stenosis of the pulmonary artery [he might have added, "or of the pulmonary valve or infundibulum"], (2) interventricular septal defect, (3) deviation of the origin of the aorta to the right and (4) hypertrophy of the right ventricle, almost always concentric in type. At times there is an additional entirely accessory defect; namely, patency of the foramen ovale.

One cannot at the present time attribute the *maladie bleue* to the persistence of the foramen ovale without direct opposition to the great majority of observed facts; when the communication between the two auricles exists alone without any other associated cardiac lesion, cyanosis does not result.

This combination of lesions is ascribed by Abbott,² largely on the basis of studies by Sir Arthur Keith, to an arrest of development before the eighth week of embryonic life.

Kurtz, Sprague and White³ have reported three cases of the tetralogy of Fallot with necropsy, in two of which the condition was

* Submitted for publication, Aug. 5, 1929.

* From the Emory University Division, Grady Hospital.

* For this article the author was awarded the Luther C. Fischer prize for the best written paper presented before the Fulton County Medical Society by a member in 1929.

* The patient was presented before the Fulton County Medical Society, July 18, 1929.

1. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot: Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, *J. A. M. A.* **92**:787 (March 9) 1929.

2. Abbott, M. E.: Congenital Cardiac Disease, in Osler and McRae: *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 613.

3. Kurtz, C. M.; Sprague, H. B., and White, P. D.: Congenital Heart Disease: Interventricular Septal Defects with Associated Anomalies in a Series of Three Cases Examined Postmortem, and a Living Patient Fifty-Eight Years Old with Cyanosis and Clubbing of the Fingers, *Am. Heart J.* **3**:77 (Oct.) 1927. The tetralogy of Fallot was found in two of the necropsies reported in this paper and more recently at necropsy (see footnote 1) in the clinical case.

diagnosed during life; the ages of these patients were 23, 11 (no pulmonic valves) and 59. Cahan,⁴ in a study of 10,333 school children, found 94 cases of heart disease, 10 of which were congenital in origin; in 1 of these, the condition was diagnosed patent interventricular septum with pulmonic stenosis. Mainzer⁵ has reported a clinical case in a man, aged 25, with 18.87 Gm. of hemoglobin per hundred cubic centimeters and 7,600,000 red blood cells. I have not been able to find any other records with or without necropsy since the recent comprehensive summary of the literature by Abbott.⁶ Her original work in the field of congenital cardiac disease and careful reviews not only have illuminated its pathogenesis and pathology, but have facilitated its diagnosis, exactitude in which is of prognostic importance. For purposes of clinical classi-

*Abbott's Clinical Classification of the Markedly Cyanotic Group (from Blumer's Bedside Diagnosis)**

Lesions	Maximum Age in Years	Number of Cases	Average Age in Years
Dextroposition of aorta with localized interventricular septal defect but no pulmonary stenosis ("Eisenmenger complex")	33	8	16
Pulmonary stenosis with interventricular septal defect and dextroposition of aorta (Tetralogy of Fallot).....	36	73	11
Cor biloculare with transposition of great trunks.....	17	2	9
Pulmonary atresia with defect of interventricular septum and patent ductus	13	24	3
Transposition of arterial trunks with Interventricular septal defect and patent ductus.....	16	15	2½
Persistent truncus arteriosus (complete defect of aortic septum) with localized defect of interventricular septum.....	12	24	2

* Order based on degrees of oxygen-unsaturation and duration of life in recorded cases with autopsy.

fication, she has tabulated according to their pathologic bases the conditions that result in marked cyanosis. It is this group only that need be considered here.

Patients with marked cyanosis are sometimes highly intelligent,¹ but more often they are stunted mentally as well as physically. In cases of long-continued cyanosis there is an adaptation of the cells of the body to a subnormal supply of oxygen. The low oxygen tension apparently leads to an accumulation of toxic metabolites in the body tissues of

4. Cahan, J. M.: The Incidence of Heart Disease in School Children, J. A. M. A. **92**:1576 (May 11) 1929.

5. Mainzer, Fritz: Analyse eines kongenitalen Herzfehlers (zugleich ein Beitrag zur Bedeutung der Haemoglobinvermehrung bei Sauerstoffmangel), Ztschr. f. klin. Med. **108**:489, 1928.

6. Abbott, M. E.: The Diagnosis of Congenital Cardiac Disease, Part II, True "Morbus Caeruleus," in Blumer, Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, vol. 2, p. 430; Ventricular Septal Defects, *ibid.*, p. 420. These monographs of Dr. Abbott's have provided most of the introductory material in this paper.



Fig. 1.—Fundus oculi: duskiess, neuroretinitis and increase in number of vessels.

those regions in which the circulation is poorest. There is also an increase in the number of patent capillaries with dilatation of their lumina, which may be seen in the retina, associated at times with neuroretinitis. This accumulation of waste products and the increase in capillary volume seem to be the chief causes of clubbing of fingers and toes.

There is also compensatory increase in the number of red blood cells. In cases of pronounced polycythemia, orthostatic albuminuria may occur, as well as epistaxis, hemoptysis and even hematemesis. Vaquez and Bordet (Abbott) stated the belief that the presence of more than

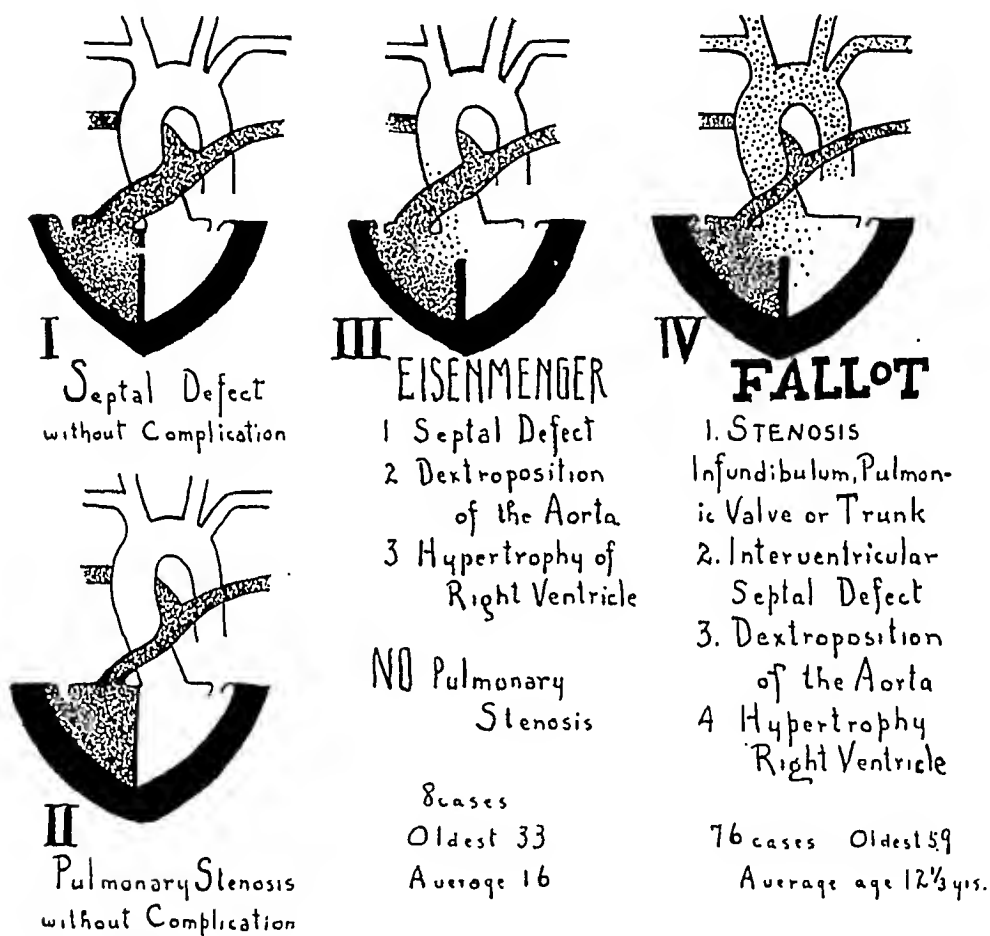


Fig. 2.—Diagram of the pathology of the tetralogy and of allied conditions.

6,000,000 erythrocytes is a grave omen. However, Wintrobe and Miller⁷ found in a study of 100 healthy medical students, aged 19 to 30, that the number of erythrocytes averaged 5,850,000, with two counts (7,350,000 and 7,530,000) above 7,000,000. The hemoglobin in this series ranged from 13.4 to 18.3 Gm. per hundred cubic centimeters of blood, averaging 15.87 Gm.

As Fallot observed, uncomplicated patent foramen ovale does not cause cyanosis. Interventricular septal defect alone is often of little

7. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929.

clinical significance, and does not cause cyanosis without failure of the left ventricle. Pulmonary stenosis with intact interventricular septum may not cause cyanosis or other symptoms for the first ten or fifteen years of life. A slightly patent ductus arteriosus rarely causes symptoms or cyanosis, and a widely patent one is associated with other anomalies incompatible with life beyond early infancy. In brief, marked cyanosis of long duration in the case of an adult is almost certainly due either to the tetralogy of Fallot, or to the "Eisenmenger complex," which is the same thing except that there is no pulmonic stenosis.

Cases of the tetralogy, in addition to the invariable deep cyanosis and clubbing from earliest infancy, often present a thrill and harsh systolic murmur just to the left of the sternum. These are usually maximal in the second interspace; it has been maintained that when the murmur is loudest below this that the stenosis is infundibular rather than pulmonic, but exception has been taken to this view.⁸ The murmur is usually well transmitted to the vessels of the neck. In the majority of instances the area of cardiac dulness is markedly increased above and to the right, but in some, in spite of great hypertrophy of the right ventricle, this is not made out, owing to the rotation of the heart on its vertical axis. Enlargement of the right ventricle and often increased breadth of the ascending aorta may be seen in the roentgenogram. The electrocardiogram shows right ventricular preponderance and increased amplitude of the P-waves and sometimes of the T-waves as well. The differential diagnosis, then, is virtually a question of the size of the pulmonary outlet. When there is no stenosis at this orifice, cyanosis may not develop until late, thrills are absent, murmurs are not transmitted above the base of the heart, and roentgen examination reveals hypertrophy of the conus pulmonalis. A typical case of the "Eisenmenger complex" has recently been communicated by Baumgartner and Abbott.⁹

It has been shown¹⁰ that in one type of cardiovascular anomaly syphilis is not more common than in the general population; it is not therefore an etiologic factor in that condition. It has not been established that syphilis is common in cases of tetralogy of Fallot.

There is no specific treatment for the tetralogy of Fallot. Every person afflicted with congenital heart disease should live within his physical limitations and, on account of the frequency of death from sub-

8. Raab, W.; Weiss, R.; Lowbeer, B., and Rihl, J.: Untersuchungen über einen Fall von kongenitalen Herzvitium, *Wien. Arch. f. inn. Med.* **7**:367, 1924.

9. Baumgartner, E. A., and Abbott, M. E.: Interventricular Septal Defect with Dextroposition of Aorta and Dilatation of the Pulmonary Artery ("Eisenmenger Complex"), Terminating by Cerebral Abscess, *Am. J. M. Sc.* **177**:639 (May) 1929.

acute bacterial endocarditis in such cases, should have all possible foci of infection removed, as has long been advocated by many authors, including myself.¹⁰

White and Mudd¹¹ have reported eight cases of angina pectoris in persons less than 30, associated in each case with aortic regurgitation of rheumatic origin, and have assembled thirty-four similar ones. In none was a diagnosis of congenital defect made. Willius,¹² it is true, has seen extensive coronary disease at necropsy in three cases of persons less than 30. In two other communications with associates in the

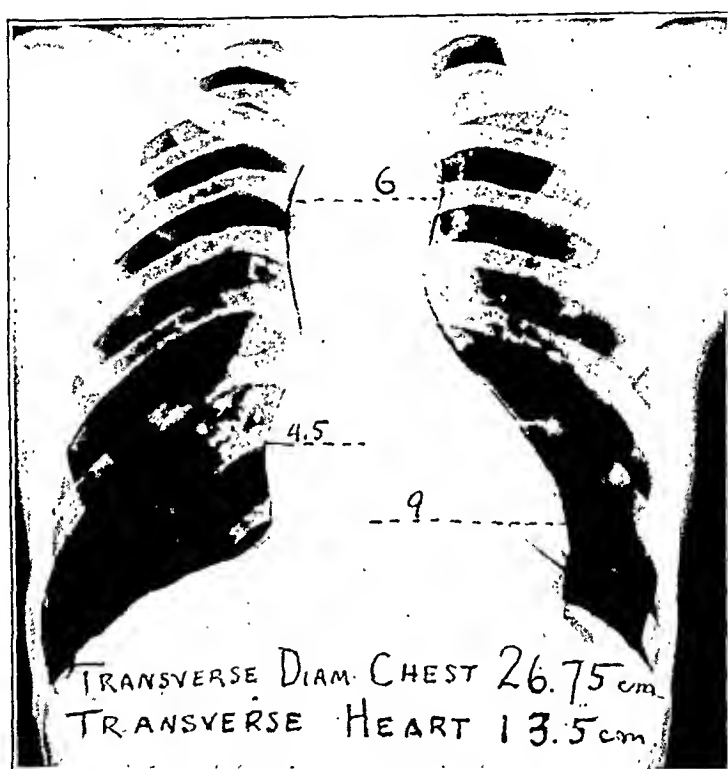


Fig. 3.—Roentgenologic appearance of heart at 7 foot tube distance. Heart shadow is round and is increased transversely owing to right ventricular enlargement. In the region of the conus pulmonalis the shadow is concave and does not show the prominence often seen in cases of patent ductus arteriosus, and always seen in cases of the Eisenmenger complex.

Mayo Clinic,¹³ Willius has expressed the opinion that cardiac pain is essentially due to "coronary circulation insufficient either in amount or

10. Blackford, L. M.: Coarctation of the Aorta, *Arch. Int. Med.* **41**:702 (May) 1928.

11. White, P. D., and Mudd, S. G.: Angina Pectoris in Young People, *Am. Heart J.* **3**:1 (Oct.) 1927.

12. Willius, F. A.: The Protean Manifestations of Disease of the Coronary Arteries, *New Orleans M. & S. J.* **80**:143, 1927.

13. Barnes, A. R., and Willius, F. A.: Cardiac Pain in Paroxysmal Tachycardia, *Am. Heart J.* **2**:490 (Dec.) 1927. Willius, F. A., and Giffin, H. Z.: The Anginal Syndrome in Pernicious Anemia, *Am. J. M. Sc.* **174**:30 (July) 1927.

in oxygen saturation." Keefer and Resnick¹⁴ have recently reviewed the whole subject of angina and have concluded that it is always due to anoxemia of the myocardium. This syndrome is rare in congenital cardiac disease.

REPORT OF CASE

History.—An illiterate negro, aged about 20, reported to the dispensary of Grady Hospital on May 10, 1929, complaining of pain over his heart. His father had died of pneumonia; his mother, four brothers and four sisters were living and



Fig. 4.—The patient.

well. He was ill with influenza during the World War, but had never been confined to bed at any other time. When he was a boy, he could run short distances as fast as his playmates, but he could never run as far on account of shortness of breath. This shortness of breath had interfered with his activities as long as he could remember, and he had never been as stout as his brothers and sisters. His nails had always been curved. He freely admitted sexual promiscuity and excesses, but had the usual ingenious, if apocryphal, explanation of a phallic lesion. The Wassermann reaction was negative at the Grady Hospital in 1928.

14. Keefer, C. S., and Resnick, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, *Arch. Int. Med.* **41**:769 (June) 1928.

When the patient was about 14 years old he secured employment in a sawmill. Unusual exertion in the mill would bring on sharp, stabbing pain, beginning near the apex of the heart and radiating up to the base. These pains were severe, but a few moments of rest would relieve them. On one occasion his shoulder was supporting one end of "a great big log" and something slipped and he had to support the log alone a few seconds; just after this he felt the most awful stabbing pain in his heart that he had ever felt, and he spit up a little blood. He had had some bleeding from the nose and had coughed up blood from time to time since, and he had observed that his sputum was always brown. About three years previous to admission he came to Atlanta to live. That year his ankles began to swell toward evening, but he had not noticed this recently. He had suffered a great deal from generalized headache, but subjective pounding of the heart had been rare. He had been working as janitor in a small apartment house for about two years. Ordinary exertion, including shoveling coal, had not bothered him much, but heavy lifting had always brought on cardiac pain. Late in April of this year

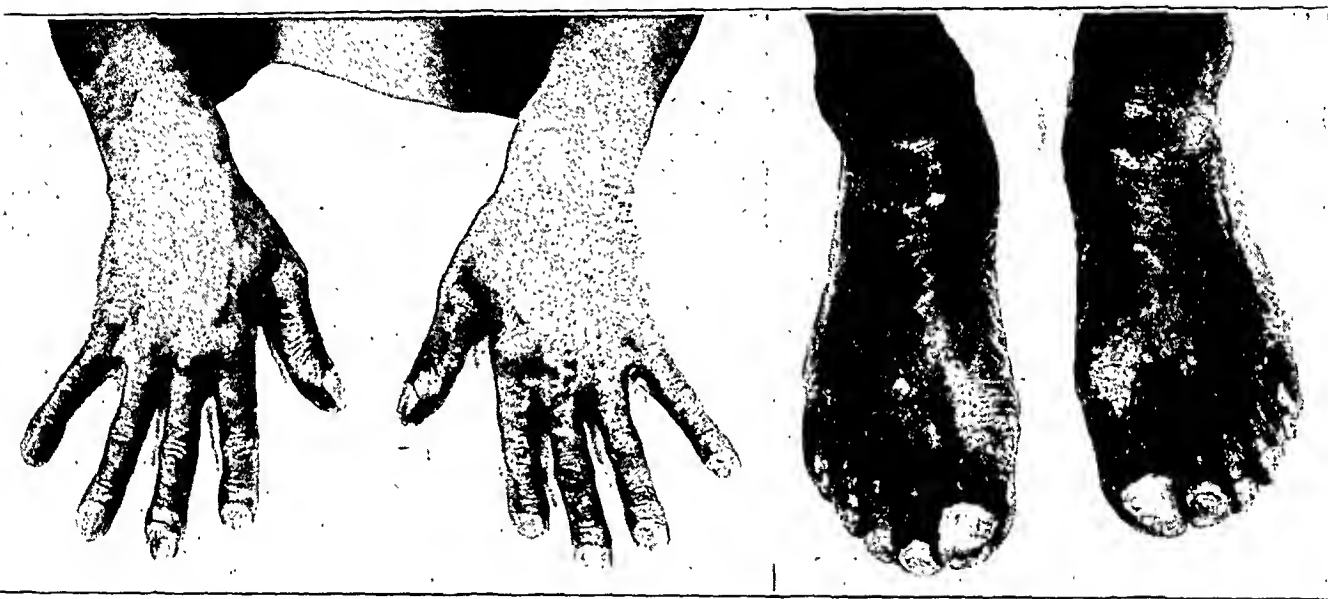


Fig. 5.—Clubbing of fingers and toes.

he carried a heavy box upstairs and was seized with agonizing pain, second only to that experienced once in the sawmill. Unlike the former seizures, this one lasted for some time, and similar attacks began to come on without undue exertion several times a day. It was on account of the frequency, severity and duration of these that he came to the clinic.

Examination.—The patient was 62½ inches (159 cm.) tall and weighed 104 pounds (47.2 Kg.). His state of nutrition and muscular development was only fairly good. The skin of the trunk was dark, but that of the head and extremities, particularly of the lips, ear lobes, fingers and toes, was almost blue-black. The interpalpebral sclerae were purplish-brown; on pulling down the lids numerous blue vessels coursing over pale blue sclerae were exposed. The inner aspects of the lips were purplish slate. Pigmentation of the mucous membranes of colored persons, particularly of the highly pigmented ones, is not unusual, but pressure on the lip in this instance drove out the purplish hue, thus proving that the color was due to profound cyanosis. The tongue was also cyanotic. Clubbing of the fingers and

toes was extreme. The teeth were in good condition. The tonsils were moderately enlarged and cryptic; the anterior cervical glands were also enlarged. The thyroid gland was of normal size and the lungs were clear. Just to the left of the sternum a "distant" thrill was palpable in the second, third and fourth interspaces, most pronounced in the fourth. Cardiac dullness extended 3 cm. from the midline in the third left interspace, 2 cm. in the fourth right interspace and 8 cm. in the fifth left interspace. A prolonged, harsh systolic murmur was heard all over the precordium, indeed all over the chest, but it was loudest in the fourth interspace at the left

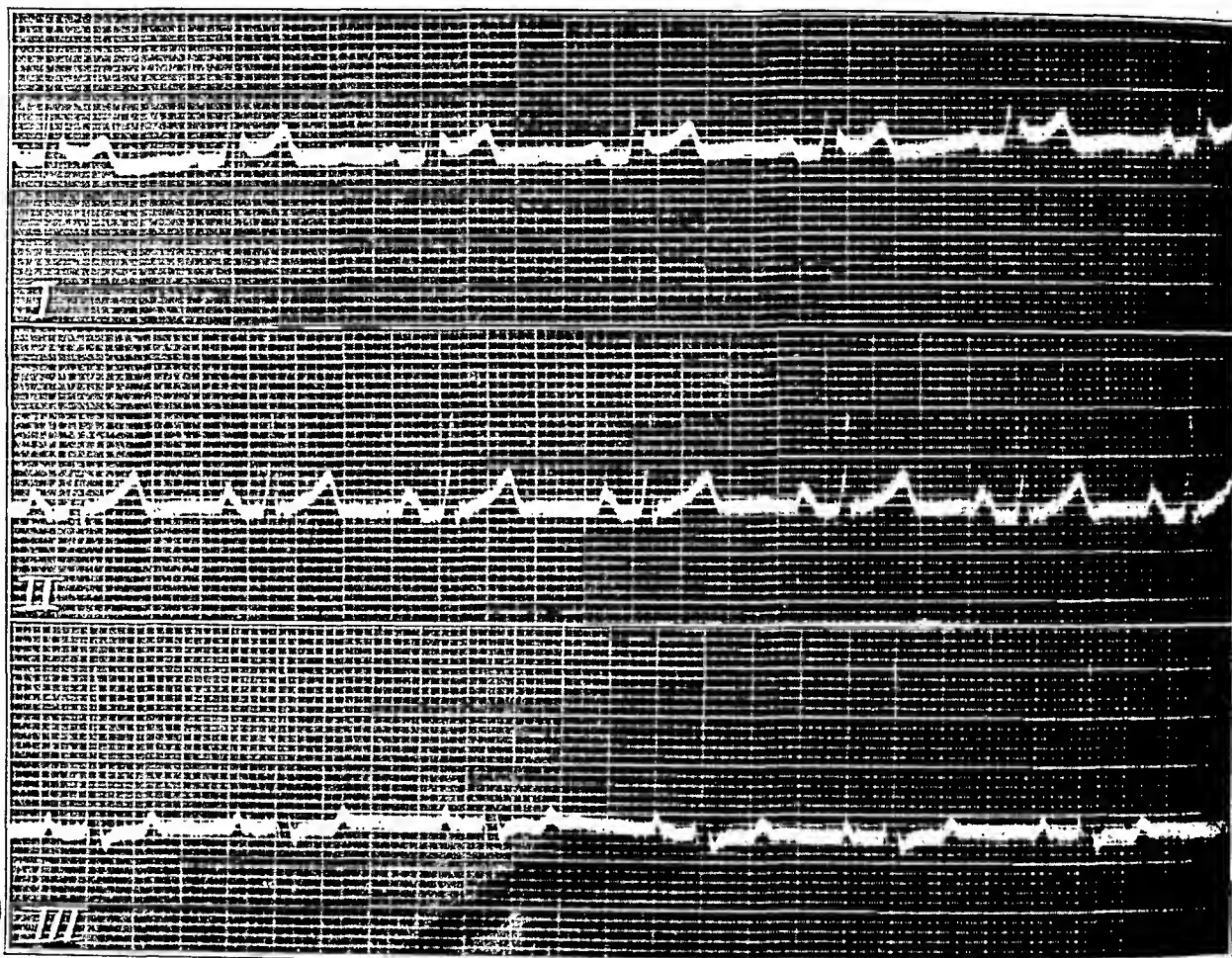


Fig. 6.—Electrocardiogram showing right ventricular preponderance and increased amplitude of the P and T waves in Leads I and II. (Courtesy of Dr. L. M. Bonner.)

border of the sternum; in the back the maximal intensity of the murmur was in the left interscapular space. There was no diastolic murmur. On palpation the prostate seemed normal. There was no evidence of edema of the extremities, and the tendon reflexes were normal. The retina was dusky, especially around the nerve-head for a radius of about three disk-diameters. The arterioles were about the color of normal retinal veins, and the veins were much darker and appeared somewhat dilated; both appeared to be increased in number. Moderate neuroretinitis was evidenced by 1 diopter of papilledema.

The blood pressure was 110 systolic and 60 diastolic (mercury manometer). During the period of observation in the hospital the pulse was usually about 60. The venous blood contained 19.4 Gm. of hemoglobin per hundred cubic centimeters (Newcomer standard), 125 per cent according to the average normal of Wintrobe and Miller. The laboratory of biochemistry reported the hemoglobin of capillary blood to be 18.5 Gm. The erythrocyte counts of the venous blood were 7,660,000 and 7,760,000 and averaged 7,710,000. The leukocytes numbered 5,950, and the differential count was normal. The first specimen of urine, voided when the patient was ambulatory, gave albumin, grade 3, no casts, 5 to 8 red cells per high power field and a few pus cells. After rest in bed albumin was graded 1, and an occasional granular cast was reported, but no red cells. The phthalein output was 60 per cent in two hours. The icterus index was 15, nonprotein nitrogen 35, creatinine 1.5 and blood sugar 101. The Wassermann reaction was strongly positive.

Dr. Lila M. Bonner said of the electrocardiogram: "There is right ventricular preponderance. The P and T waves in Leads I and II are sharp and prominent."

Dr. J. J. Clark reported concerning the teleoroentgenogram of the heart: "The transverse diameter of the inside of the thorax is 26.75 cm. The right border of the heart is 4.5 cm. from the midline, the left border 9 cm. The ascending aorta is 6 cm. wide."

Course.—After a week's rest in the hospital, the patient felt better and was released. A few weeks later, tonsillectomy was done under local anesthesia. He is now receiving mild antisyphilitic treatment and leading an inactive life. The Family Welfare Society is trying to find him suitable work; this is difficult on account of his total lack of education and training.

COMMENT

It is true that in some cases of the tetralogy of Fallot the increased width of the ascending aorta is more prominent than in this, and yet the roentgenogram in this case is strikingly like that in the case of White and Sprague. Moreover the descriptions of the physical examinations are remarkably similar; it is most improbable therefore that there is a difference in the pathologic bases of the two. In my case, however, the maximal murmur is in the fourth interspace. This may indicate that the stenosis is below the pulmonic valve, that is, that it involves the infundibulum.

As already pointed out, in cases of marked cyanosis of long standing in an adult, the diagnosis of septal defect with dextroposition of the aorta is all but certain; the differential point is the presence or absence of stenosis in the pulmonary system. In this case physical signs and the roentgenogram prove that one is not dealing with the "Eisenmenger complex." I believe therefore that in making the diagnosis of the tetralogy of Fallot the chances of error that I run are relatively few. I present this report then without waiting for necropsy, partly because Kurtz, Sprague and White first so presented theirs and also because the indigent negroes are hard to keep track of, and the prospects for ultimate necropsy in this case are accordingly not too good.

It is interesting to speculate as to the cause of the cardiac pain. At first it would seem to be syphilitic in origin. However, this patient has been suffering from this type of pain for five years or longer and, in spite of his sexual precocity, it is not probable that he had contracted syphilis at such an early age that it would be far enough advanced to cause these symptoms at 14. His numerous healthy brothers and sisters and their children constitute an argument against congenital syphilis and, finally, the negative Wassermann reaction in 1928 would indicate that he contracted syphilis but recently. It is evident that the oxygen supply to the whole body is poor; therefore I believe that this pain which comes on following exertion is due to anoxemia of the myocardium, that is, is true angina, and that this anoxemia is the direct result of the dextroposition of the aorta.

The retinal picture is striking. The increase in hemoglobin and erythrocytes is characteristic. Orthostatic albuminuria is well illustrated, as well as hemoptysis and epistaxis.

SUMMARY

A clinical case of the tetralogy of Fallot associated with angina pectoris is reported.

NOTE: Dr. R. S. Leadingham told me at the meeting of the Fulton County Society that he had recently made the diagnosis of the tetralogy of Fallot on his service at the Georgia Baptist Hospital, and has showed me his patient. Although the thorax in his case is smaller than in mine, the outlines of the hearts in the teleoroentgenograms can be almost exactly superimposed; the relative hypertrophy in his case is therefore greater than in mine and the prognosis accordingly graver. Dr. Leadingham is reporting his case elsewhere: necropsy was performed in December, 1929.

SPASM-PRODUCING SUBSTANCE IN THE SPUTUM OF PATIENTS WITH BRONCHIAL ASTHMA*

JOSEPH HARKAVY, M.D.

NEW YORK

In 1922, Zeydner and van Leeuwen¹ reported the presence of an alcohol-soluble, toxic substance in the blood of twelve persons suffering from asthma, urticaria and migraine which had a definite stimulating action on smooth intestinal muscle. The method of extraction of this substance, that of Freund,² was designed to eliminate those normal stimulating and augmentor substances which may appear in any serum during the process of clotting. When safeguarded in such a manner, this technic yielded negative results with the blood serum of normal controls, whereas a definite action was demonstrable with the serum of persons with an "allergic disposition."

The many difficulties encountered in the utilization of blood extracts with Freund's method have been emphasized by Clark and Gross,³ who showed that the substance present in normal serum has a strong stimulant action on the isolated uterus and an irregular action on the isolated intestine of the rat. This substance is also alcohol-soluble and dialyzable and therefore cannot easily be eliminated. In view of their observations, it was determined to investigate the sputum instead of the blood of the patients with bronchial asthma for spasm-producing substances. In this investigation sixteen cases of bronchial asthma and forty-three controls were employed.

EXPERIMENTAL WORK

Sputum from asthmatic patients was collected in 6 ounce bottles containing 95 per cent alcohol. Separate specimens were collected before, during and after an attack of asthma. The sputum was allowed to stand overnight, and on the following day it was shaken and filtered through coarse filter paper. The alcohol filtrate was then evaporated at a temperature not exceeding 56 F., and the residue which had a yellowish resinous appearance was dissolved in 10 cc. of Tyrode's solution.

* Submitted for publication, Sept. 28, 1929.

* From the Laboratories of the Mount Sinai Hospital.

1. Zeydner and van Leeuwen, W. Storm: Occurrence of a Toxic Substance in the Blood in Cases of Bronchial Asthma, Urticaria, Epilepsy and Migraine, *Brit. J. Exper. Path.* 3:6 (Dec.) 1922.

2. Freund, H.: *Arch. f. exper. Path. u. Pharmacol.*, vol. 91, p. 272.

3. Clark, A. J., and Gross, L.: The Action of Blood on Isolated Tissues, *Arch. internat. de pharmacod.* 28:243, 1923-1924.

This sputum extract was tested for spasm-producing properties on isolated intestines of cats and of rabbits which had been prepared as follows: A segment of the jejunum from a cat was opened, the mucosa was stripped, and a piece of muscle one-half inch in length was suspended in a bath of Tyrode's solution at 37 C. which was supplied with a constant stream of oxygen. The muscle was attached to a lever which recorded its contractions on a slowly revolving drum. Whenever a rabbit's intestine was employed, about three fourths of an inch of the intact gut obtained from the duodenum or from the jejunum was used. Frequently before and after each experiment the relative contractility of the gut was ascertained by testing its response to 0.005 mg. of pilocarpine.

TABLE 1.—*The Effect on Cats' Intestine of Alcohol-Soluble Extracts from Sensitive Asthmatic Patients*

Patient	Sensitive to	Spasmophilic Reaction of Sputum
1—D	Chicken feathers	Positive
2—Deg.	Goose feathers.....	Positive
3—M. v. D. B.	Oat infested with mites.....	Positive
4—F.	Dust	Positive
5—B. W.	Dust	Positive
6—B.	Horse dander and dust.....	Positive
7—B.	Horse dander.....	Positive
8—O.	Horse dander.....	Positive

TABLE 2.—*The Effect on Rabbits' Intestine of Alcohol-Soluble Extracts from Sensitive Asthmatic Patients*

Patient	Sensitive to	Spasmophilic Reaction of Sputum
9—A. C.	Ragweed, goose feathers, timothy.....	Positive
10—C. S.	Cottonseed, chicken and pigeon feathers.....	Positive
11—R.	Rabbit hair, sheep wool.....	Positive
12—G.	Timothy	Positive
13—C. P.	Timothy and ragweed.....	Positive
14—F.	Plantain, timothy and ragweed.....	Positive
15—D.	Horse dander, dog hair, timothy, sheep wool.....	Positive
16—D.	Plantain and Hudson seal.....	Positive

When it was definitely established that the muscle strip was functioning properly, from 1 to 2 cc. of the sputum extract was introduced into the bath, and the results were recorded on the revolving drum. In the first two of the earliest cases the unextracted sputum was obtained during the patient's attack. The muscular contraction produced by this sample which was diluted in 10 cc. of Tyrode's solution was prompt and sustained. In order to exclude the presence of derivatives of split proteins brought about by the action of bacteria on the proteins in the bronchial secretions, which might be responsible for a stimulating action on the suspended muscle, only alcohol-extracted sputum was used in subsequent experiments.

The first series of experiments was performed on cats' and the second on rabbits' intestines. The latter, as seen in the illustrations, is not so suitable for this work as the former. This is evidenced by the weaker contraction of the rabbits' strip

as compared with the cats'. A definite contraction of the segment after the introduction of the intestinal strip indicated a negative reaction.

RESULTS

The alcohol-soluble extracts from sixteen allergic, asthmatic patients invariably produced spasm of both rabbits' and cats' intestine in vitro (tables 1 and 2). Variations in the degree and promptness of the reaction occurred following the use of sputum extract from different cases. This is best shown in the illustrations.

TABLE 3.—*Effect on Rabbits' and Cats' Intestines of Alcohol-Soluble Extracts from Nonsensitive Asthmatic Patients*

Patient	Diagnosis	Spasmophilic Reaction of Sputum
R.	Pansinusitis	Negative
Br.	Suppurative ethmoiditis.....	Negative
R.	Bilateral suppurative ethmoiditis.....	Negative
F.	Chronic bronchitis and tuberculosis.....	Negative
K.	Pansinusitis	Negative

TABLE 4.—*Control Cases*

Diagnosis	Number of Cases	Reaction
Tuberculosis	8	Negative
Bronchiectasis	4	Negative
Bronchitis	1	Negative
Pulmonary neoplasm.....	1	Negative
Valvular disease.....	6	Negative
Healthy subjects.....	5	Negative
Resolving pneumonia.....	4	Negative
Sinus infection.....	1	Negative
Grip	1	Negative
Colitis	1	Negative
Abscess of lung.....	6	Negative
Acute lobar and bronchopneumonia.....	5	Positive

The sputum of five nonsensitive, asthmatic patients did not contain a smooth, muscle-stimulating substance (table 3).

Thirty-eight control subjects gave no evidence of any spasmophilic substance comparable to that found in the sputum of allergic asthmatic patients (table 4).

The sputums of five patients with acute lobar pneumonia and bronchopneumonia contained a smooth, muscle-stimulating substance (table 4). These sputums, however, were sanguineous, and since the blood-free sputums of four cases of resolving pneumonia gave negative reactions, it is reasonable to attribute the spasmophilic property to the

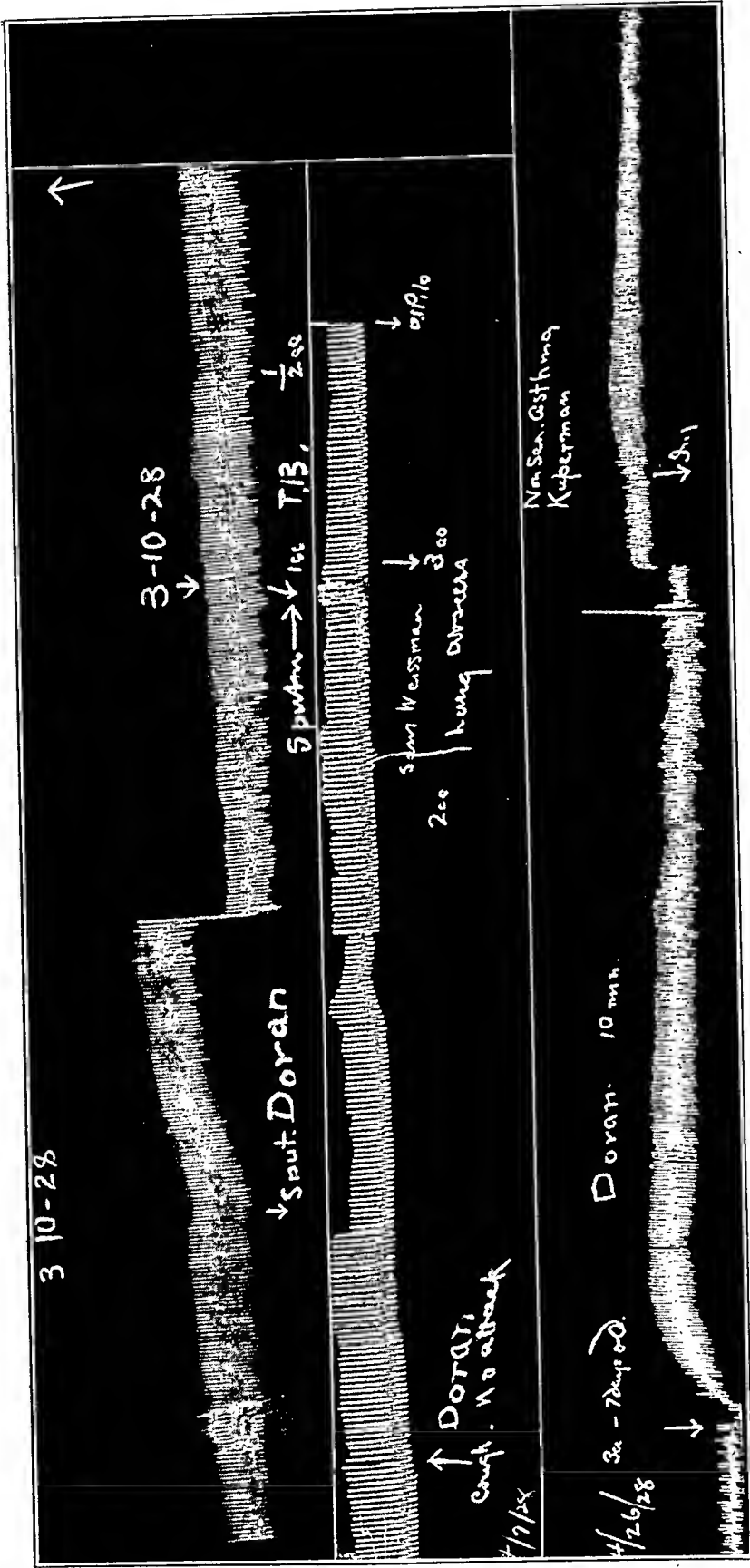


Fig. 2.—D. was sensitive to horse dander, dog hair, timothy and sheep wool. The first asthmatic attack that was investigated occurred on March 10, 1928. The extract of sputum at this time produced a definite contraction of the rabbits' intestine. On April 7, the patient was free from attacks, and the sputum presented no demonstrable spasmophilic substance. On the same strip of muscle, sputum from a case of abscess of the lung and one of pulmonary tuberculosis also gave negative reactions. On April 26, the patient developed another attack. The sputum that was obtained was introduced into the water bath, and the drum was allowed to run ten minutes. The picture presents a progressively increasing contraction of the intestinal strip, both the amplitude and the height of contraction gradually subsiding at the end of the period. On the same strip, a case of nonsensitive asthma was tested and a flat curve is evident.

SUMMARY AND CONCLUSIONS

The sputum of sensitive, asthmatic patients contained an alcohol-soluble substance which is capable of stimulating the contraction of smooth muscle. This substance was absent from the sputum of non-sensitive, asthmatic subjects and of those without asthma. The rusty sputum of patients with lobar pneumonia and with bronchopneumonia gave a positive reaction, but the effect may be attributed to the presence of blood, as blood-free sputum from patients with resolving pneumonia gave no reactions. The exact nature of the spasm-producing substance in the sputum was not elucidated.

CORRECTION

In an article by M. M. Wintrobe on "Blood of Normal Young Women Residing in a Subtropical Climate," which appeared in the February issue, an error occurred in the heading for table 4 on page 300. This should read "Observations on the Blood of Healthy Young Women from 17 to 30 Years of Age in Different Parts of the World."

THE ANEMIAS OF SPRUE

THEIR NATURE AND TREATMENT *

BAILEY K. ASHFORD, M.D.

SAN JUAN, PORTO RICO

Twenty-four cases of sprue, with a pernicious type of anemia, were studied for the purpose of contrasting these with cases with a non-megaloblastic type of anemia, some of which were not even due to sprue.

Before consideration of these particular cases, it is necessary to state the classification on which they are based in this paper. The anemias are considered as falling into one of two divisions: (1) the nonmegaloblastic, or so-called "secondary" anemias, and (2) the megaloblastic, medullary or "primary" anemias. The distinction between these two forms of anemia has always been readily recognized in hematology, but the advent of liver as the therapeutic agent for the treatment of patients with megaloblastic anemia has brought with it a ready means of further dividing the pernicious anemias into those which yield a definite rise in reticulocytes and those which do not produce this phenomenon after treatment. For convenience, and because it seems rational, I have found it useful to divide these "pernicious" types of anemia into (1) dysplastic, (2) hypoplastic and (3) aplastic types.

The reasons for these designations are based on the pathologic observations and the clinical evidence after the use of liver in treatment. Granting that the reticulocyte is an immature erythrocyte, the product of the mother cell, the megaloblast, and further granting that in this type of anemia the megaloblast lacks some as yet undefined substance found in highest concentration in the liver, to enable it to give birth to young erythrocytes, it is proposed that von Biermer's term "dysplastic anemia," which implies the true pathologic state involved, be adopted for those cases of anemia heretofore termed pernicious, or primary, in which a well defined shower of reticulocytes occurs following the use of liver or some adequate extract.

What happens in hypoplastic anemias is more or less a matter of conjecture, but whether the marrow is overcrowded with megaloblasts,

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as in the former case, which in spite of this undefined stimulus have failed to respond, or whether there has been a great reduction in the number of megaloblasts to a point far below normal and the numbers still remaining are insufficient, notwithstanding the stimulus, to produce a well defined rise in the number of reticulocytes in the circulating blood, the fact remains that one is justified in using the term hypoplastic in those cases in which liver preparations have failed to produce a shower of reticulocytes.

As for the aplastic anemias heretofore found in younger people and generally conceded to be a rare form of pernicious anemia, the only possible justification for the diagnosis can be found in a biopsy or in the death of the patient and the examination of the bone-marrow histologically. While clinically an aplastic anemia may be suspected, it must be remembered that many patients with the hypoplastic type die without reaching the point at which one fails to find megaloblasts in the osseous medulla, or at which only a negligible number are found.

So much for the anatomic facts. Now as to the pathogenesis. When the marrow fails to replace the blood elements lost in circulation, a state of exhaustion of the hemopoietic organs is established which nature tries to remedy by multiplying the number of megaloblasts. Whether or not this condition is originally due to lack of that mysterious something which the liver particularly furnishes is immaterial, as in the end there is an insufficient nutrition of the mother cell, the megaloblast. Certain poisons other than that produced in idiopathic pernicious anemia can bring about an anemia which is pernicious. A pernicious anemia is seen at times in severe uncinariasis, in *bothriocephalus* anemia, in streptococcic anemia, and, as will be shown in this paper, in the anemias of sprue. Of course, the particular poisons generated in each of these distinct clinical entities must be more or less different, albeit more or less similar; hence there are small or moderately well defined differences in the hematologic picture, as modified by specific toxins in each. One can hardly expect the hypothetical toxin of the typical addisonian anemia to produce a clinical, or even a hematologic, picture identical with that produced in sprue; but what seems to be fundamental is that all anemias which bring about a failure of the hemopoietic organs rest on a fairly uniform pathologic condition of the bone-marrow and must be classified on this basis alone, namely, a failure of the megaloblasts to produce a sufficient brood of new erythrocytes to replace a steady and finally overwhelming loss of the blood elements in circulation.

On this conception, the term "pernicious anemia" not only should not be rigidly limited to that particular form which has always been considered classic, to the original addisonian anemia, but should be definitely eliminated as vague and unscientific.

In this series of anemia, sixteen cases have developed during the course of sprue, and all but one of these were megaloblastic in type.

Eight of the sixteen were cases of dysplastic anemia, of which six yielded a definite rise in the number of reticulocytes after the administration of liver extract prepared by Lilly and Company. In one case the patient yielded weak rises in the number of reticulocytes during the period of inoculation by *Monilia psilosis* vaccines, and one patient responded to the use of the sprue diet almost as vigorously as did those given liver extract, although the curve was totally different and more prolonged. Seven of the sixteen cases of sprue anemia were hypoplastic in type; of these, only one showed a rise in the reticulocytes, and that rise was feeble and ineffectual while the patient was taking liver extract. In only one of the sixteen cases was the condition accompanied by a true secondary anemia, and it, incidentally, has been one of the most obstinate under treatment. The eight cases of anemia due to other causes than sprue were all nonmegaloblastic; and in all there was no rise in the number of reticulocytes in spite of doses of the same liver extract which were similar to those given for the treatment of the dysplastic and hypoplastic types of anemia.

As to results of treatment in the cases of dysplastic types of anemia, all but one of the patients were clinically cured during a period varying from about two to five months. In the excepted case, the patient, while distinctly improved, is still in a severe condition due to the fact that she has failed to adhere to her diet, chiefly because of poverty. In only three of the eight cases of dysplastic anemia was there an erythrocyte percentage between 80 and 90; and these percentages were reached in fifty-six, seventy-seven and one hundred and sixty-seven days, respectively. In the eighth case, the rise was presumed to have occurred before the administration of liver extract was started. By rough calculation, the average number of days required for liver extract to effect a rise in the reticulocytes was five, the extremes being two and nine. The days consumed in effecting a rise in the reticulocytes from less than 2 per cent to the peak averaged three; the extremes were one and six. The days required for the percentage of reticulocytes to fall from the peak to below 2 were six, the extremes being two and fourteen. The total time during which the reticulocytes were above 2 per cent was ten days; the extremes were four and twenty.

While these figures are insufficient for scientific deduction, they suggest that, in order to measure the effect of liver extract in dealing with a case of megaloblastic anemia, percentages of reticulocytes should be estimated at least twice a week in order to be fairly sure of noting a rise.

Of the hypoplastic types, I may begin by criticizing the diagnosis in three of seven cases, for in only four can it be proved that a previous rise in the reticulocytes had not occurred before the administration of liver extract was begun. The diagnosis of hypoplastic anemia,

however, has been based not only on the lack of rise in the reticulocytes, but on the entire course, which demonstrates a slow and painful clinical improvement under adequate treatment. It must be remembered that liver extract was not available for administration until Jan. 1, 1928.

The secondary anemias due to other causes than sprue are herein included for the sake of contrast, and the charts and histories would seem to serve the purpose intended. In only two cases was there any suggestion of sprue.

THE MEGALOBLASTIC ANEMIA OF SPRUE

The Price-Jones Curve.—The enormous amount of work involved in measuring the erythrocytes once a week was accomplished by my assistant, Miss Luz M. Dalmau, who also made all of the differential counts of leukocytes and many of the erythrocyte and leukocyte counts. Our joint conclusions follow.

In an article by J. R. Bell, F. K. Thomas and J. H. Means,¹ a study is made of the diameter of the red cell in twenty normal persons and in twenty-five suffering from pernicious anemia. These investigators used arithmetical probability sheets for plotting the curve of the diameter of the red cell, and calculated thus the double dispersion, which is a correct measure of anisocytosis, by subtracting the value in microns at the point where the curve cuts the 16 percentile grade from the value at the point where it cuts the 84 percentile grade. The median is the point in the curve where it cuts the 50 percentile grade; at this point there are as many cells of a larger diameter on one side as there are of a smaller diameter on the other. The median, consequently, shows whether the cell population tends to be of greater or less diameter than that of the usual normal. These authors found that normally the range of the median lies between 7.4 and 8 microns, with an average of 7.7, and that the median about corresponds to the mean diameter. They found that normally there was a dispersion of from 1 to 1.2, the average being 1.1.

In twenty-five cases of pernicious anemia, they found an average median of 8.6 and an average dispersion of 2.3 microns, the maximum being 3.6 and the minimum, 1.4. The largest red cell found by them in pernicious anemia was 13.9 microns, and the smallest, 4. They emphasized the fact, first enunciated by Price-Jones himself, that increased dispersion plus increased mean diameter is highly characteristic of the red cells in pernicious anemia.

In our series of cases, measurements are correct up to 1 micron; in theirs, up to 0.625. In our series, weekly measurements were made

1. Bell, J. R.; Thomas, F. K., and Means, J. H.: Studies on Red Cell Diameter; In Health and in Pernicious Anemia, J. Clin. Investigation **3**:229, 1926.

of only 100 red cells for each case. Thus it will be seen that our routine and instruments were not set at so high a standard as that employed by the aforementioned authors. But it would seem that these imperfections are too small to warrant the sacrifice of time and expenditure of energy involved in their method; time, number of cases and extremely limited personnel being considered.

The outstanding features in our cases of megaloblastic anemia seem to be:

1. During the time before treatment has modified the blood picture, there is apt to be great disparity between the mean and median, the latter being nearly always of a much higher value. This phase is referred to on the chart as the first period. In cases in which the blood picture is not greatly modified throughout the whole course, the first period is merely the first half of the case.

2. In that phase in which the blood values are probably affected by treatment (referred to on some charts as the second period), the value of the median descends to or near that of the mean, although the double dispersion remains little affected. This may not be a characteristic of the megaloblastic anemias of sprue alone, but it can be seen to be an outstanding fact in our twenty-four cases. Moreover, we do not recall having seen it mentioned heretofore in studies made of addisonian anemia.

3. Notwithstanding the tendency of the median to approximate the mean as a result of treatment or of a spontaneous favorable turn in the course of the disease, the double dispersion in both periods remains fairly constant. That is the same as saying that after apparent cure, or at least after a more or less complete regression of all symptoms and a return to nearly if not normal erythrocyte and hemoglobin percentages, the degree of anisocytosis is only slightly reduced, and the mean still remains above normal.

4. While the average mean in our cases was about that cited for idiopathic pernicious anemia by the three authors already mentioned, maximum diameters of red cells in our series frequently exceeded those found by them. N. Rosenthal of New York, on looking over some of our slides, stated it to be his impression that the cells in our cases were larger than those in idiopathic pernicious anemia. Of course, what he referred to was what Price-Jones so happily terms "the pernicious element in the red cell population." On one occasion, not recorded in this series, a cell measuring 22 microns was encountered.

5. The inspection of the plotted curve in our cases shows that what really changes in the blood picture for the better is the skewness of the curve; in other words, as the patient improves, the fascicle of curves for two months, let us say, is smoother and more even. This is, in fact,

about the only difference; for, as I have said, the mean and double dispersion are practically unchanged.

The Nucleated Red Cell in the Medullary Anemia of Sprue.—A decided statement can be made to the effect that normoblasts and megaloblasts in the circulating blood are not common. They were found in only three of the sixteen cases of megaloblastic anemia, and then in small numbers.

The Form of Erythrocytes.—I do not recall having seen a statistical account of the relative frequency of oval forms of erythrocytes in any considerable number of cases of idiopathic megaloblastic anemia. Nevertheless, of eleven cases of this type of anemia due to sprue, three yielded 80 per cent or more of perfectly round cells; six, from 60 to 79 per cent; and only two, 44 and 54 per cent, respectively. Thus it will be seen that the majority of erythrocytes are round. As the patient improved, the percentage of round cells increased from 93 to 100.

White Cell Count.—Of fifteen cases of megaloblastic anemia of sprue, six gave normal white cell counts; two rose from normal to leukocytosis; one fell from normal to leukopenia; five gave leukopenia, of which three rose to leukocytosis and one to normal, one remaining leukopenic; and one presented leukocytosis throughout the course of treatment. It is justifiable to state that, in 50 per cent of the cases, leukopenia is present at some time during the course of the anemia, and a rise to a mild leukocytosis with the patient under treatment is frequent.

Varieties of Leukocytes in the Megaloblastic Anemias of Sprue.—In general, it may be said that the striking distortion of the normal differential count lies in the relative lymphocytosis at the expense of the neutrophils, and in the eosinophilia so frequently observed after the use of liver extract in dysplastic anemia. In the eleven cases which possess differential counts at more or less equal intervals, however, the aforementioned vagaries from the normal are by no means consistent at stated periods. In order to bring out a contrast between the as yet uninfluenced blood picture and the leukocyte formula at the end of the case, it was decided to make an average of the percentages of each variety of cell during the first month of treatment, and compare it with that of the last month.

The average percentage of neutrophils at the beginning of these cases was 51.8; at the end, 64.6; the average leukocyte percentage, 40.4 and 27.2, respectively; the average eosinophil percentage was 3.8 and 5.8, respectively. Thus, though these figures, in general averages, substantiate the rule, the observations in three of the cases are distinctly against the rule so far as the neutrophil-lymphocyte relationship is concerned. Moreover, when a rise in the number of eosinophils is noted with the patient under treatment, I find that there are only three cases in which a distinct increase can be noted.

An inspection, however, of the detailed blood charts shows marked rises in eosinophils after the first month of observation, which fall and often disappear during the last month. Obviously, therefore, the entire series of observations must be taken into consideration, not merely those of the first and last months. Considering, accordingly, the whole percentage curve for each of the three varieties of leukocytes, at some time or other during the course of treatment, ten cases, or 91 per cent, presented a relative lymphocytosis. The place to look for the evidence of eosinophilia is in the middle of the curve and not at the extremities. Eight patients, or 72.7 per cent, showed it at some time during the course of treatment; and in four cases, or 36 per cent, it was marked. I am therefore justified in stating that a well defined relative lymphocytosis and eosinophilia at the expense of the neutrophils occurs in from three fourths to nine tenths of the cases of megaloblastic anemia due to sprue, in which the patients are under treatment with liver extract.

In 1903, Ashford and King,² reporting on the anemias of uncinariasis, stated that "after treatment in chronic cases and those in the later stages of the disease, a rise in eosinophils may be expected, and is of good prognostic import. It may be due to a more active regeneration in the bone marrow. . . . When, however, there is a fall of eosinophils, accompanied by lack of improvement in physical signs, death may often be the result."

Thus, twenty-five years ago, this same eosinophil phenomenon presented itself in the severe anemias accompanying uncinariasis.

CASES ILLUSTRATIVE OF THE TYPES OF ANEMIA FOUND IN SPRUE

While only sixteen cases of the anemia of sprue have been closely studied, I have had many more which for one reason or another are incomplete, but which are complete enough to permit of a fairly sound diagnosis as to the type of anemia; and from all the evidence so far accumulated it seems justifiable to say that in not more than one half of the clinical cases of sprue in which the patients present themselves for medical attention is there any considerable anemia. Indeed, I have had several cases of severe sprue with practically no anemia in which the outcome was fatal. Thus, it is clear that the belief that severe sprue and pernicious anemia are one and the same disease seems unwarranted. The real type of megaloblastic anemia to be expected in severe sprue is hypoplastic. From all I can gather from my confrères who are studying idiopathic pernicious anemia in the United States—a disease which does not appear to be frequent in Porto Rico, and which

2. Ashford, Bailey K., and King, W. W.: A Study of Uncinariasis in Porto Rico, *Am. Med.* 6:391 and 431 (Sept. 5 and 12) 1903.

I have not seen in that country—the type is almost invariably dysplastic, and the rise in reticulocytes after the administration of liver or some adequate extract thereof is prompt, sharp and high. There seem to be more nucleated erythrocytes, and there may be still other although unimportant differences.

TABLE 1.—*Measurements of One Hundred Erythrocytes in Case 1*

Date	Diameter in Microns															Maxi- mum	Mini- mum	Mean	Median	Disper- sion
	2	3	4	5	6	7	8	9	10	11	12	13	14	15						
2/20	..	1	3	7	11	12	23	26	12	3	2	12	3	7.95	9.3	2.5	
2/27	1	3	1	7	5	12	19	15	19	13	3	1	..	1	15	2	8.48	10.4	3.3	
3/6	4	4	7	10	27	25	20	3	11	4	8.22	8.5	2.8	
3/13	4	10	13	31	25	15	1	..	1	13	5	8.18	8.4	2.9	
3/22	3	3	10	36	29	17	2	..	1	13	5	8.57	8.5	2.9	
3/26	1	3	11	40	32	10	3	11	5	8.41	8.3	2.4	
4/2	2	16	48	30	3	1	11	6	8.19	8.1	2.3	
4/20	1	2	16	60	15	6	10	5	8.04	7.8	2.0	
5/10	1	4	23	48	16	7	1	11	5	7.99	8.0	2.2	
6/4	6	14	49	22	9	6	8.15	8.6	2.3	
7/9	2	11	42	22	20	3	11	6	8.56	8.1	2.8	

Blood Counts

Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho-nuclears	Lymphocytes	Monocytes	Eosinophils	Basophils	Plasmocytes	Metamyelocytes	Myelocytes
2/20	35%	1,248,000	3,000	55.3	31.3	0.6	10.6	..	1.2	0.6	..
2/22	34%	1,544,000	61	33	...	3	3	..
2/27	61	33	...	3	3	..
2/29	43%	1,912,000	61	33	...	3	3	..
3/1	45%	61	33	...	3	3	..
3/2	46%	61	33	...	3	3	..
3/6	49%	2,248,000	9,000	51	40	...	5	4	..
3/8	70%	51	40	...	5	4	..
3/9	65%	2,936,000	81	11.5	...	7	0.5	..
3/13	81	11.5	...	7	0.5	..
3/17	81%	3,376,000	42	45	...	6	2	..	5	..
3/22	85%	3,968,000	42	45	...	6	2	..	5	..
3/26	3,976,000	49	32	1	6	1	..	11	..
3/29	79%	3,992,000	49	32	1	6	1	..	11	..
4/2	79%	3,760,000	8,200	68	22	...	8	..	1	1	..
4/5	87%	68	22	...	8	..	1	1	..
4/9	87%	3,888,000	8,200	47	43	1	7	...	1	1
4/16	83%	4,688,000	47	43	1	6	1	1	1	..
4/20	4,408,000	47	43	1	6	1	1	1	..
4/26	92	47	43	1	6	1	1	1	..
4/30	95%	4,656,000	38	52	1	7	...	1	1	..
5/10	38	52	1	7	...	1	1	..
5/11	88%	4,704,000	4,200	38	52	1	7	...	1	..
5/22	91%	5,080,000	38	52	1	7	...	1	1	..
6/4	90%	5,496,000	9,000	65	26	...	8	1
7/9	89%	4,112,000	70	20	5	4	...	1

Form of Erythrocytes

Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
2/20	82.5%	17.5%	4/2	87%	7%	6%
2/27	75%	25%	4/20	97%	3%
3/6	86%	13%	1%	5/10	95%	5%
3/13	88%	11%	1%	6/4	96%	4%
3/22	95%	5%	7/9	95%	5%
3/26	95%	4%	1%				

The following cases are detailed in order to bring out the principal points previously mentioned.

CASE 1.—*Dysplastic Anemia of Sprue*.—F. V., a white man, a Dominican, aged 59, was first seen on Feb. 20, 1928. His normal weight was 147 pounds (66.7 Kg.); his present weight was 122 pounds (55.3 Kg.). He had gone to Paris two years

previously to consult well known authorities concerning a persistent "indigestion" with anemia. He was supposed to be suffering from the effects of a malarial infection which had started five years before, although examinations of the blood failed to reveal the parasite. Treatment failed to improve his condition, and he sought medical advice in New York. Complete physical and laboratory examinations were made, but the mass of data acquired merely demonstrated a secondary anemia and hyperacidity of the gastric contents. No diagnosis was made. The patient then had a lobar pneumonia. On recovery, he decided that he had sprue and appeared in Porto Rico. The hemoglobin content was 34 per cent and the patient was profoundly cachectic.

Clinical analysis revealed incomplete sprue with absence of the characteristic tongue but a typical intestinal syndrome. The patient was placed on the standard diet for patients with sprue, digestive aids, strychnine, oxide of magnesia and calcium carbonate, and was directed to take six vials of liver extract a day. A month later this patient was greatly improved, especially the condition of his blood, but the picture of sprue at times recurs, with excess of intestinal gas, and occasional diarrhea.

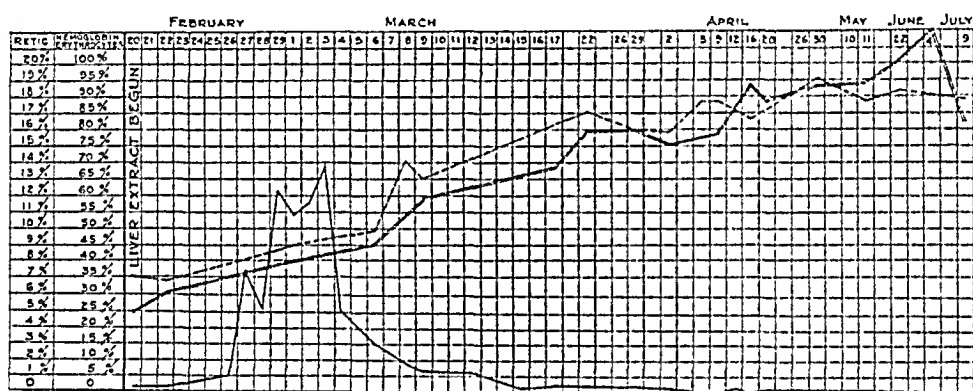


Chart 1 (case 1).—In this and in charts 3, 5, 7, 9 and 11 the single line is the curve of the reticulocytes the percentage of which is indicated in the first column; the double line is the percentage of erythrocytes to a normal fixed at 5,000,000 per cubic millimeter, and the broken line is the percentage of hemoglobin, both of which are indicated in the second column.

Comment.—This was a case of tropical sprue with a veiled clinical picture. When the patient was seen in Paris and New York, the anemia was distinctly of the secondary type. It became medullary after an attack of severe pneumonia and was the outstanding feature on his arrival in Porto Rico. With the solution of the hematologic problem, the intestinal syndrome came out clearly, and still remains, although it is much less severe.

At the time of admission to the hospital the erythrocytes numbered 1,248,000; they rose steadily and rapidly to 5,080,000 in three months. The number of reticulocytes rose sharply in about a week after the administration of liver extract was begun, and dropped to normal in ten days. There were no normoblasts, and 25 per cent of the cells were oval or irregular; this percentage fell to 5 per cent after four months.

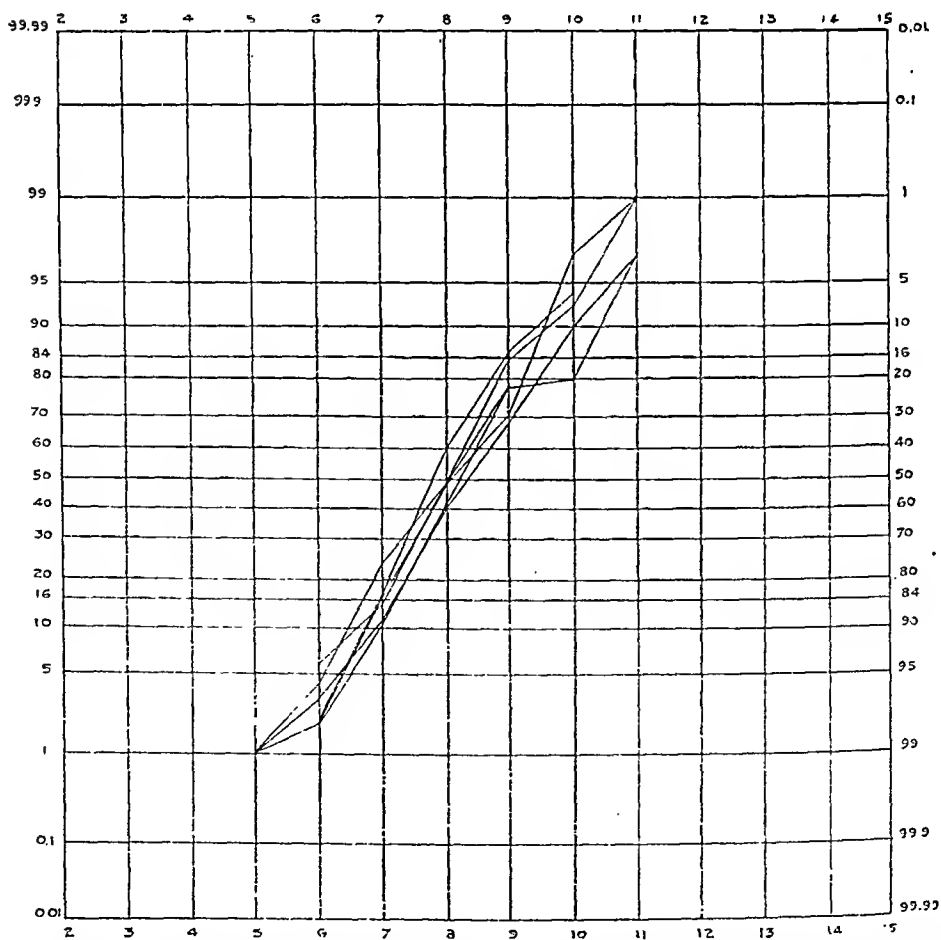
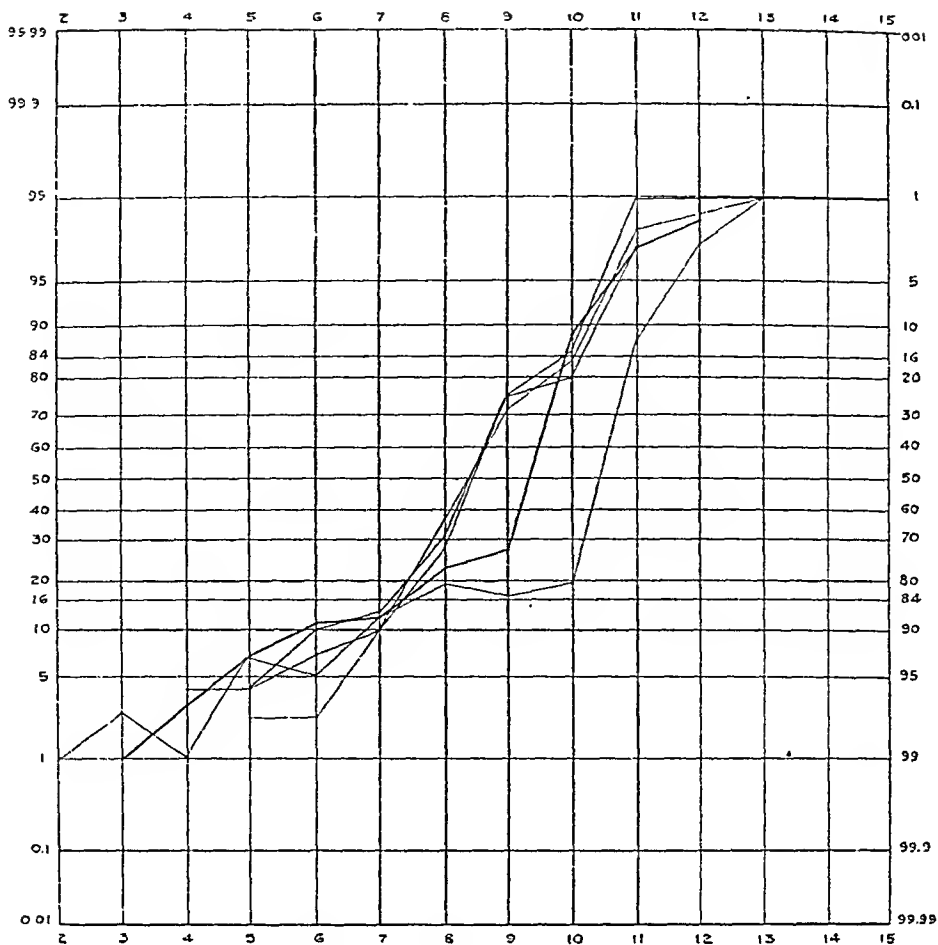


Chart 2 (case 1).—The upper chart shows curves for first period to March 22 inclusive; the lower chart, those for the second period from March 26 to July 9, inclusive.

At first there was leukopenia; later the leukocyte count was normal. A moderate relative lymphocytosis was observed during the course of treatment, as well as a slight eosinophilia.

There was a disparity at first between the means and the medians; after this they tended to blend. The skewness of the curve was noticeable during the first period; this tended to disappear during the second period.

TABLE 2.—Measurements of One Hundred Erythrocytes in Case 2

Date	Diameter in Microns										Maximum	Minimum	Mean	Median	Dispersion
	5	6	7	8	9	10	11	12	13	14					
2/ 3	1	3	6	25	30	29	6	11	5	8.9	9.5	2.9
2/10	7	9	6	23	15	19	15	3	12	5	8.6	8.4	1.4
2/17	..	1	8	32	33	21	2	3	12	6	8.8	9.4	2.8
2/22	..	4	9	15	25	32	10	5	12	6	9.2	10.3	2.8
2/28	..	3	7	23	32	27	8	11	6	8.9	9.4	2.8
3/13	1	9	20	39	19	10	1	1	12	5	8.0	8.2	2.8
3/23	1	3	3	30	37	21	5	11	5	8.8	9.3	2.6
3/30	..	5	16	43	26	8	1	1	12	6	8.2	8.2	2.5
4/17	..	2	10	40	35	13	10	6	8.4	8.4	2.6
4/27	9	42	28	19	2	11	7	8.6	8.2	2.4

Blood Counts

Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho-nucleurs	Lymphocytes	Monocytes	Eosinophils	Basophils	Plasmocytes	Metamyclo-cytes	Myelocytes
12/ 3	22%	460,000	1,400
12/ 7	14%	392,000	1,700	24	73	..	3
12/23	30%	1,290,000	3,000
12/28	33%	1,392,000
1/ 2	30%	1,216,000	3,350
1/11	36%	1,136,000	3,680
1/23	37%	1,552,000	4,550
1/31	44%	1,640,000	4,600	64	24	4	8
2/ 3	35	31	20	11	3	..
2/ 7	43%	1,824,000	5,600
2/10	56%	56	10	1	28	5	..
2/16	68%	2,392,000	5,540	56	26	4	12	2	..
2/21	69%	2,264,000	2,400	59	18	5	17	1
2/28	80%	2,408,000	6,400	55	23	2	12	8	..
3/ 1	75%	3,104,000
3/13	89%	3,176,000	8,800	47	21	1	25	1	..	5	..
3/20	92%	3,128,000	..	55	22	..	18	2	..	3	..
3/30	79%	3,560,000	..	40	45	..	10	5	..
4/17	93%	4,048,000	12,700	69	21	..	8
4/21	..	3,584,000
4/27	100%	3,972,000	..	50	41	1	8
7/ 5	100%	3,832,000	..	50	39	3	8

Form of Erythrocytes

Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
2/ 3	65%	23%	7%	3/20	92%	8%	..
2/10	75%	23%	2%	3/30	91%	7%	2%
2/17	80%	19%	1%	4/17	90%	7%	3%
2/28	77%	22%	1%	4/27	94%	4%	2%
3/13	91%	7%	2%	7/ 5	93%	5%	..

CASE 2.—*Dysplastic Anemia of Sprue*.—L. B. C., a white man, Porto Rican, aged 56, an overseer on a coffee plantation, was seen on Dec. 3, 1927. I had treated this patient ten years previously for sprue, and he had promptly recovered and remained well for seven years. Three years before the present examination he began to suffer from indigestion, and at the present time had the most profound anemia that I have seen accompany sprue, with a hemoglobin of 13 per

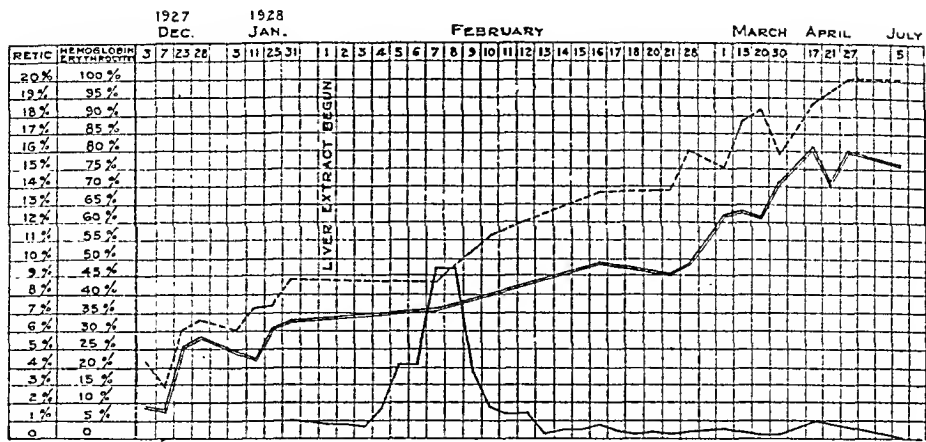


Chart 3 (case 2)

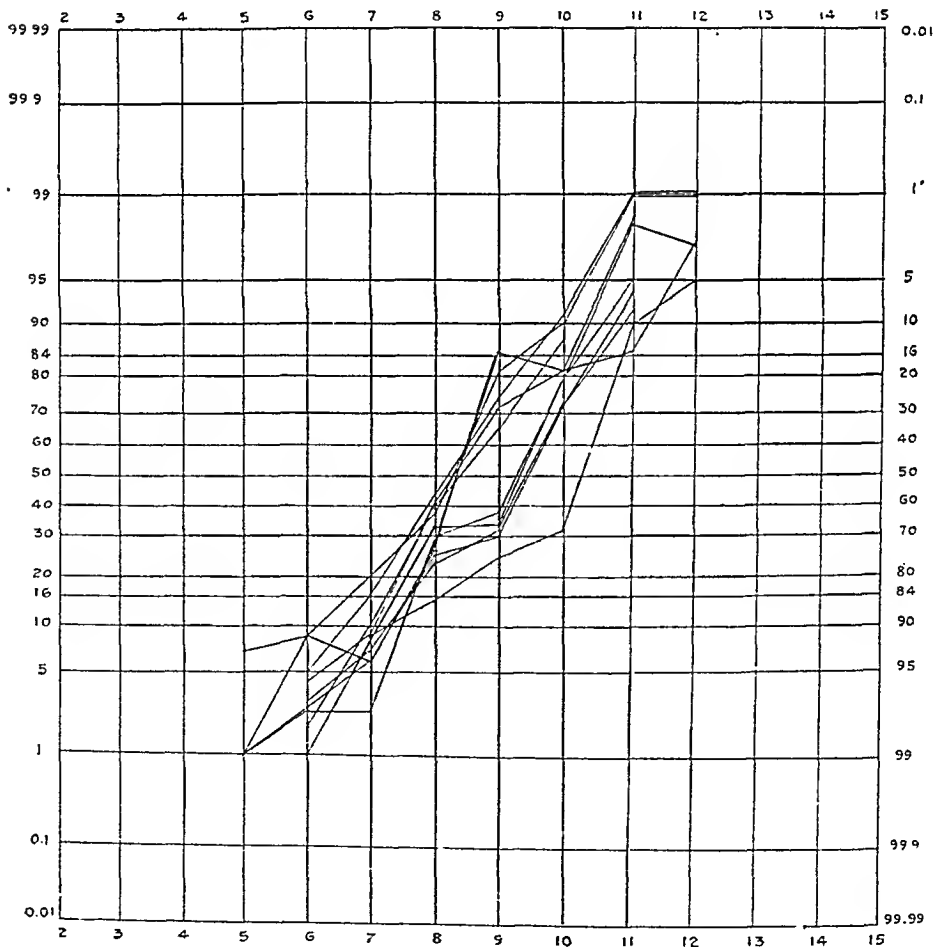


Chart 4 (case 2)

cent, 8 per cent erythrocytes and asthenia so great as to require his being carried into my office by two men. The picture of sprue was complete and typical. At the beginning of treatment the patient weighed 110 pounds (49.9 Kg.), his normal weight was 145 pounds (65.8 Kg.).

He was placed on the standard diet for sprue and told to eat 1 pound of liver a day. This diet, with digestive aids, tonics and symptomatic remedies, was kept up for two months, with considerable improvement in the patient's general condition, a prompt disappearance of the leading symptoms of sprue, and a gain of 1,250,000 erythrocytes per cubic millimeter and 31 per cent hemoglobin. He was then given six vials of liver extract a day from February 1 to 5, and thereafter three vials a day. After a month and a half of this additional treatment, he had gained 45 per cent in hemoglobin and 1,536,000 erythrocytes. He had a good color, was seemingly well, and did a vigorous day's work without fatigue.

Comment.—Fifty-nine days of an unusual quantity of liver in this patient's diet did not prevent a sharp rise in the reticulocytes on the subsequent administration of liver extract. As in all other cases, the color index is still high and the hematologic picture is still of a pernicious type.

Four days after admission the red cells numbered 392,000 and steadily rose throughout five months to 4,048,000. The reticulocytes rose sharply three days after the first administration of liver extract, and fell again to normal in three days. There were no normoblasts, and on admission 28 per cent of the red cells were oval or irregular; at the last blood reading they were 5 per cent.

When the patient was admitted, he had a leukopenia, his white cells numbering 1,400; when he was discharged, he had a leukocytosis, his white cells numbering 12,700. When he began treatment he had an extremely high lymphocytosis; under treatment pronounced eosinophilia occurred, eosinophils rising from 3 at the time of admission to 28 per cent.

During the first period a marked skewness occurs which disappears in the second. In the second period the means and medians blend, but it will be observed that the dispersion is about the same in each period.

CASE 3.—*Dysplastic Anemia of Sprue.*—M. R., a married woman, a mulatto, aged 23, was first seen on March 28, 1928. Her mother died of thyroid disease, and her sister, residing with her, had the same disease as herself. Up to 6 years before the present examination, she was healthy and well. At the time of admission she weighed 81 pounds (36.7 Kg.), though her normal weight was 125 pounds (56.7 Kg.). She stated that she had never suffered from indigestion. The disease began suddenly with vomiting and diarrhea, and within two or three days she had a raw tongue with white, foamy, intestinal movements. She had no appetite, and suffered from enormous gaseous distention of the intestine. One of the features in this case was nausea and vomiting, and there had been a great excess of saliva, alternating with dryness of the mouth. She was nervous, extremely weak, had severe myalgic pains and palpitation of the heart. There was marked numbness of the extremities, great depression of spirits and severe cramps in the legs. The mental apathy in this case was unusually marked, and

the patient seemed to be in a confused state of mind. She was deathly pale, with an addisonian tint of the skin, and she stated that she had not menstruated for eight months, although she was not pregnant.

The patient was placed on the sprue diet, but in spite of the rise in reticulocytes, the blood values persistently remained the same, although she steadily

TABLE 3.—Measurements of One Hundred Erythrocytes in Case 3

Date	Diameter in Microns												Maxi- mum	Mini- mum	Mean	Median	Disper- sion
	3	4	5	6	7	8	9	10	11	12	13						
3/28	1	2	4	12	16	34	23	9	1	1	..	12	3	7.8	8.4	2.4	
4/ 4	1	4	6	15	29	27	12	5	1	11	3	7.2	7.5	2.6	
4/10	1	6	11	26	23	22	7	4	10	3	6.7	6.5	3.0	
4/18	..	1	2	4	18	21	27	16	6	5	..	12	4	8.6	9.4	3.1	
4/27	8	9	24	28	19	11	1	..	12	6	8.7	9.4	2.9	
5/ 1	..	1	3	16	28	38	11	1	10	4	7.2	8.2	2.9	
5/ 8	1	..	2	20	16	26	19	14	1	1	..	12	3	7.8	8.5	3.7	
5/14	3	12	12	27	20	19	2	5	..	12	3	8.3	8.5	2.8	
5/23	..	3	3	10	11	25	20	2	1	12	4	8.2	9.5	2.8	
6/ 4	..	2	5	19	23	29	9	13	10	4	7.5	8.3	3.1	
6/ 6	..	1	4	7	9	31	21	21	1	4	1	13	4	8.4	8.4	2.8	
7/25	1	5	14	53	15	10	2	11	5	8.1	7.8	1.9	

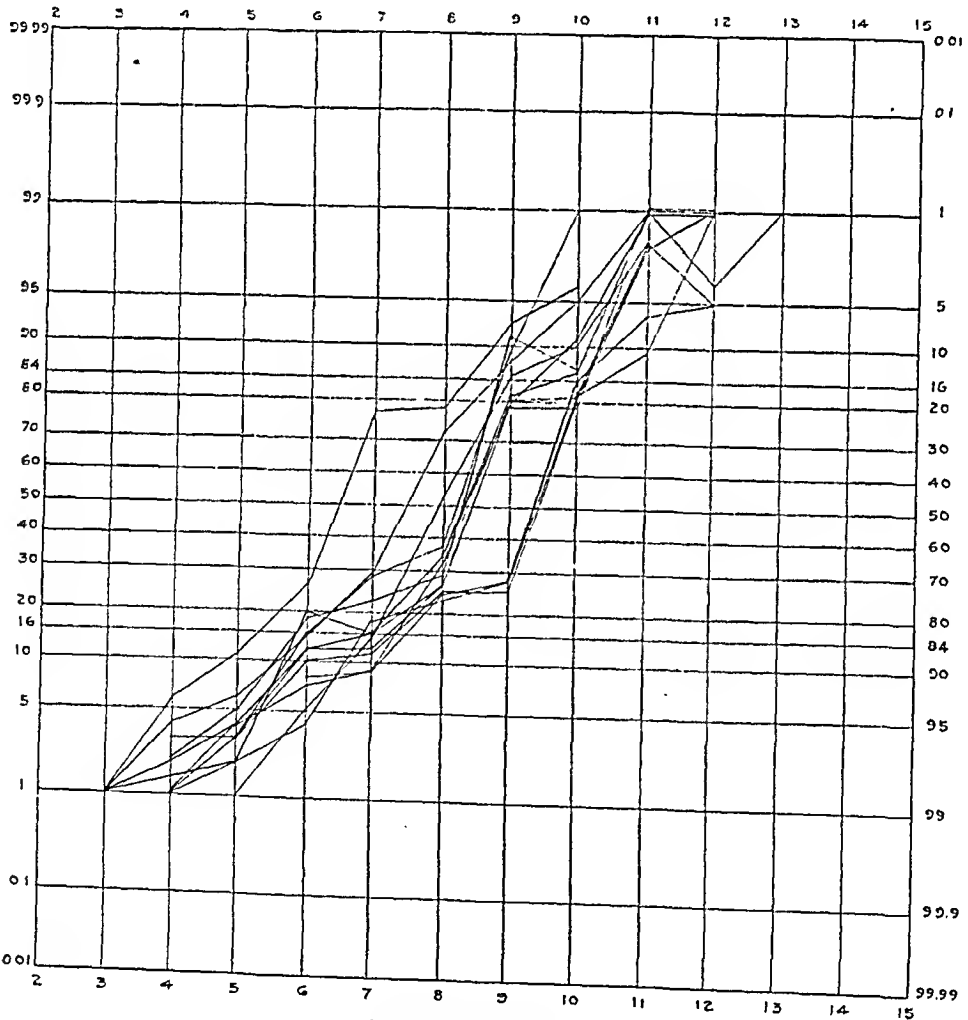
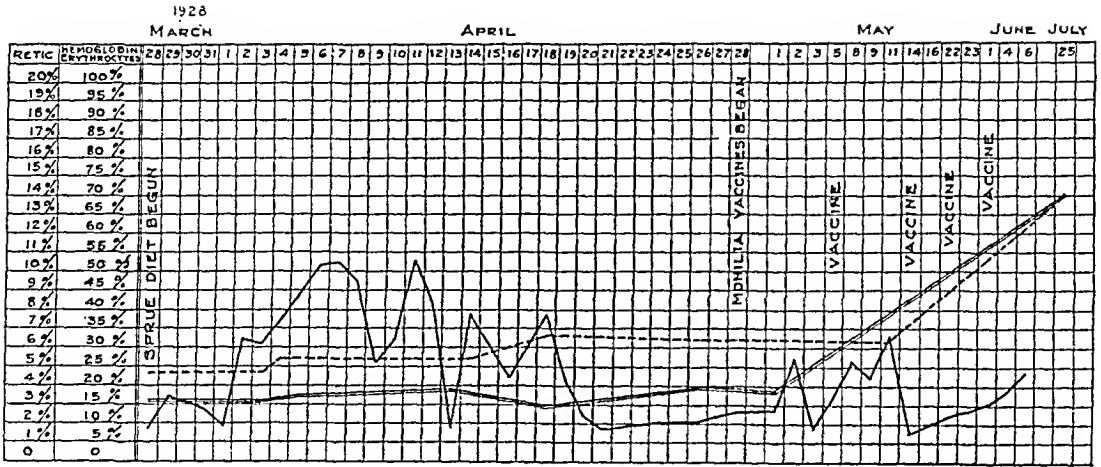
Blood Counts										
Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho- nuclears	Lymphocytes	Monocytes	Eosinophils	Basophils	Plasmocytes	Metamycelo- cytes
3/28	23%	824,000	6,200	57	38	..	1	1	..	1
4/ 3	23%	776,000	5,000	56	44
4/ 5	27%	872,000
4/10	54	44	2
4/13	..	960,000	3,600
4/14	27%
4/18	33%	728,000	3,600	60	35	2	3
4/26	32%	944,000	..	40	60
4/28	32%
5/ 1	33%	904,000	4,520	46	44	..	6	..	2	..
5/11	33%	50	46	..	4
5/23	75	23	..	2
6/ 4	58	38	..	4
6/ 6	38	60	..	2
7/25	70%	3,500,000	..	77	23

Nucleated Erythrocytes per 100 Leukocytes					
Date	Normoblasts	Megaloblasts	Date	Normoblasts	Megaloblasts
3/28.....	10	9	4/27.....	5	1
4/10.....	5	5	5/ 1.....	0	0
4/18.....	1	8	5/ 8.....	17	2

Form of Erythrocytes							
Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
3/28.....	44%	54%	2%	5/ 8.....	74%	25%	1%
4/ 3.....	54%	43%	3%	5/14.....	65%	33%	..
4/10.....	78%	21%	1%	5/23.....	55%	42%	3%
4/18.....	73%	23%	4%	6/ 4.....	88%	12%	..
4/27.....	47%	51%	2%	6/ 6.....	51%	49%	..
5/ 1.....	76%	17%	7%	7/25.....	93%	7%	..

improved. The diarrhea, sore tongue and excess of gas promptly disappeared. As no improvement was noted in the blood, she was given one tenth of a 1 per cent suspension of a killed culture of *Monilia psilosis* by inoculation on May 1, and this was repeated on May 14. No benefit resulted, although there was again a rise in the reticulocytes.

On June 5, she disappeared, both physician and patient having become wearied by these apparently unfruitful efforts at treatment, but throughout all this period,



and up to the last time I saw her, she had faithfully kept her diet. No liver was consumed by her at any time during or before this period, nor was any liver extract given. On July 25, I remarked to Dr. West of Columbia University that I had a case in which the patient had not improved on my diet, and offered her for experimentation for testing out a liver extract fraction on which he was working. I was surprised, on looking her up, to find a healthy, fat, rosy-cheeked woman weighing 125 pounds (56.7 Kg.). The patient was cured.

Comment.—This case seems to offer some striking evidence tending to demonstrate the capacity of the standard sprue diet for producing a similar effect in the pernicious type of anemia in sprue to that produced by liver in the idiopathic pernicious anemia of the North. Taken with the evidence brought forward in case 4, it further shows that an increase in reticulocytes may follow the injection of a foreign protein, in this case *Monilia* vaccines.

On the patient's admission to the hospital, the red cells numbered 824,000; four months later, they numbered 3,500,000. The reticulocyte curve was different from that produced by liver extract; it began five days after the sprue diet was started and then sluggishly rose and fell, extending over a period of nearly three weeks and being marked by brusque intermissions. The secondary rises seem to have been produced by *Monilia* vaccines. The normoblasts reached 75 per hundred thousand red cells; microblasts, 68 per hundred thousand. On admission, the oval and irregular cells formed 56 per cent of the total number; at the last reading, the percentage had fallen to 7.

The leukocytes were normal in number, but there was a high lymphocytosis and a slight eosinophilia with the patient under treatment, the eosinophils rising from 1 per cent on admission to 6 per cent.

The Price-Jones curve presented a typical skewness throughout, except the last tracing which was straighter. This case is notable for its relative microcytosis from the first. There was a high double dispersion, 3.05 microns, three months after treatment had been begun; six weeks later, the mean had fallen to normal. It is curious that this, the most microcytic in type of all of our cases of medullary anemias, should present the largest red cell ever seen by us, 22 microns.

CASE 4.—Dysplastic Anemia of Sprue.—D. F., a white woman, a Porto Rican, aged 26, married, without children, was first seen on March 5, 1928. The patient had always been strong and healthy up to three months previous to admission to the hospital, when she had an attack of acute sprue. She presented the typical picture of a severe type of the disease. Her normal weight was 120 pounds (64.4 Kg.); her weight at the time of admission was 100 (45.4 Kg.). Mental apathy was marked, and she had severe cramps in the legs and numbness of the extremities.

The favorable effect of the standard diet was explained to the patient, but she informed me that she was unable to buy anything but rice, beans, lard and codfish, with the usual cheap condiments. I then proposed that she allow me to

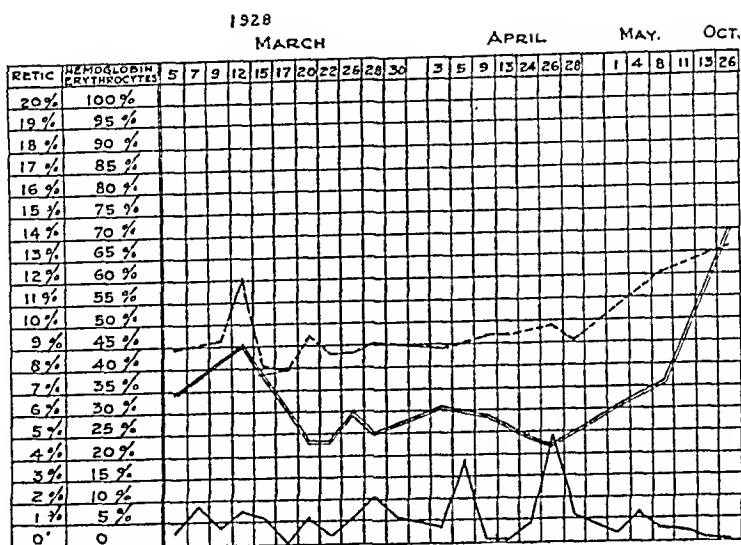


Chart 7 (case 4)

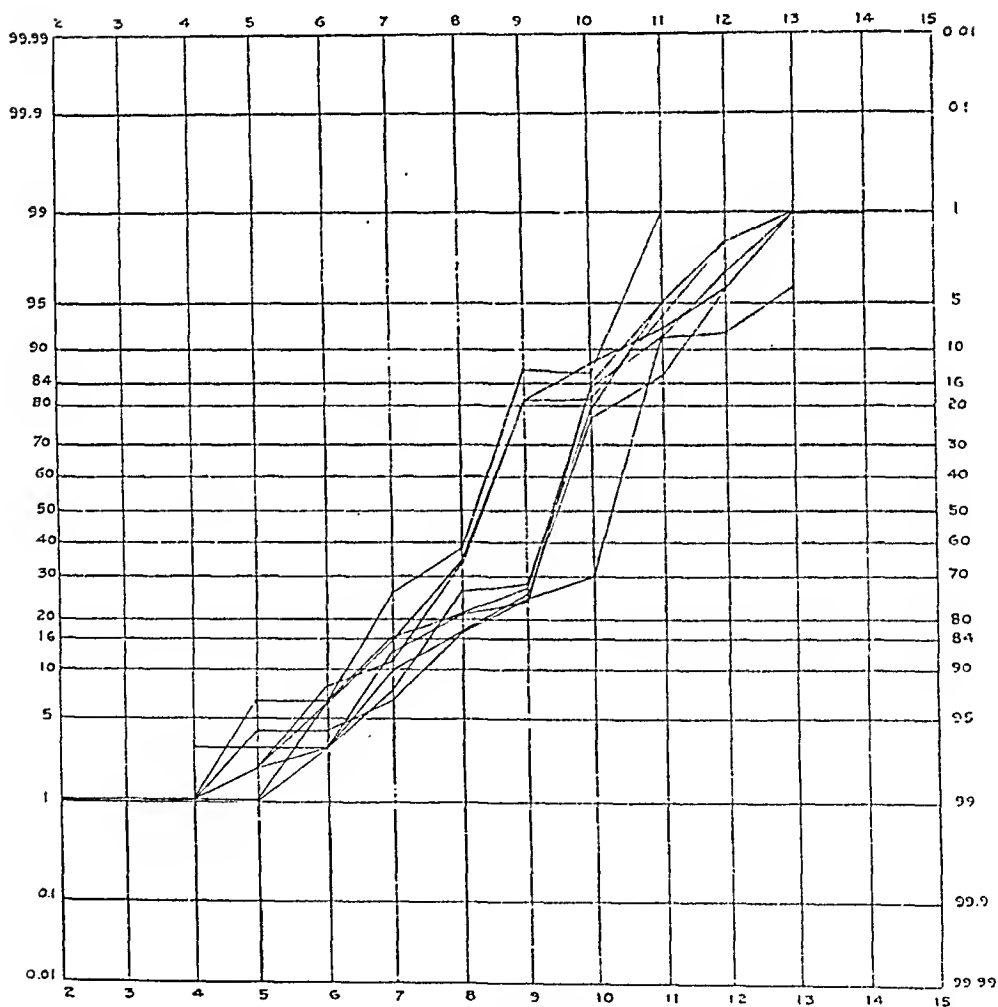


Chart 8 (case 4)

experiment on her with *Monilia* vaccines, to which she readily agreed. The contract was that she should eat all the fats, cereals and sweets that she could obtain. Vaccines were given weekly by inoculation, beginning with 0.1 cc.; the dose was increased at each subsequent inoculation by 0.1 cc. until 1 cc. had been injected, in a total of ten inoculations. After the third injection, she reported that she felt much better, and her apathy and confusional state of mind had disappeared. At this time also it was noted that the tongue had become normal, and the diarrhea and excess of intestinal gas had disappeared. On the second or third day after each inoculation, however, the buccal and intestinal picture reappeared for about twenty-four hours. After the fifth injection, her mental condition seemed normal, the sprue picture had been effaced, and the skin became softer and of a better color. Notwithstanding all this, the blood values and body weight refused to rise, and on May 11 she weighed 96 pounds (43.5 Kg.) and hemoglobin content was 46 per cent. As by this time she was wearied of her visits to me, which involved a journey of mile and a half on foot, she failed to return.

Just as I was completing the report of this case for the International Congress of Tropical Medicine, I discovered her address, sent for her on October 26, and was rewarded by finding that she had apparently recovered. Her weight had reached 116½ pounds (52.8 Kg.), and the improvement in her blood may be seen in the charts. She said that she had taken no treatment since her visits to my office, and that she had continued to eat as before, but unfortunately the obvious deduction permissible in this case is vitiated by her statement, on cross-examination, that she had eaten half a pound of liver a day for the first three weeks after she had been last seen by me.

Comment.—In evaluating the effect of *Monilia* vaccines in this case, four things seem clear: 1. The picture of sprue disappeared promptly after the third inoculation and never returned. 2. There was a slight but unmistakable, although irregular, reticulocyte response to the inoculation of the vaccines. 3. These inoculations appeared to produce an ephemeral picture of sprue. 4. There was no apparent improvement in the patient's blood values and weight during the period in which she was receiving vaccines.

As to the effect of a half pound of liver daily for three weeks subsequent to her cessation of visits to my office, the natural deduction would be that the liver was the cause of the rise in weight and blood values; but as patients in other cases of dysplastic anemia have failed to respond so favorably to liver feeding, it is reasonable to suppose that the vaccines may have had something to do with the final result. No specificity, however, is claimed, as the most natural conclusion would be that the reaction had followed the injection of a foreign protein.

The first two erythrocyte counts, a week apart, were 1,720,000 and 2,282,000, respectively. Thereafter, for six weeks, the counts were between 1,100,000 and 1,500,000. Five months later, the count was 3,496,000. There were 8 normoblasts per hundred thousand red cells. On admission there were 32 per cent oval or irregular red cells; this

rose to 93 per cent of round cells on the occasion of the last blood reading.

On one occasion, leukopenia was present. A marked lymphocytosis developed during the course of treatment. There was a mild eosinophilia of 8 per cent at the beginning, which became high as the case terminated.

TABLE 4.—*Measurements of One Hundred Erythrocytes in Case 4*

Date	Diameter in Microns																Maxi- mum	Mini- mum	Mean	Median	Disper- sion
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16						
3/ 5	1	..	1	4	4	7	17	25	30	8	2	1	13	2	8.8	10.3	2.9	
3/12	1	1	6	15	35	19	12	7	4	12	4	8.4	8.3	2.2	
3/19	2	2	2	10	17	24	23	14	4	1	1	14	4	9.1	9.5	2.9	
3/26	2	3	13	21	24	17	8	7	4	1	16	5	9.1	9.4	2.7	
4/ 3	1	2	8	11	32	19	19	6	2	12	4	8.4	8.4	2.9	
4/ 9	1	6	6	16	21	26	16	5	2	1	13	4	8.3	9.4	3.0	
4/24	1	3	15	26	29	21	5	11	5	8.6	9.4	3.1	
10/26	2	6	26	38	13	14	1	11	5	8.0	8.5	2.9	

Blood Counts

Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho- nuclears	Lymphocytes	Monocytes	Eosinophils	Plasmocytes	Basophils	Metamyelo- cytes	Myelocytes
3/ 5	44%	1,720,000	65	34	1
3/ 9	46%	2,282,000	55	36	..	8	1	..
3/12	60%										
3/15	40%										
3/17	39%		9,000								
3/19	60	34	1	4	1	
3/20	47%	1,192,000									
3/22	43%	1,184,000									
3/23	43%	1,496,000	59	46	2	1	1	
3/23	45%	1,240,000									
4/ 3	44%	1,512,000	73	25	2	
4/ 9	47%	1,416,000	65	31	1	1	2	
4/13	47%										
4/24	1,216,000	3,150	36	59	..	5				
4/26	49%	1,120,000									
4/28	45%										
5/ 1	1,523,000	8,200								
5/ 8	60%	1,776,000									
10/26	66%	3,496,000	71	10	..	16		3		

Nucleated Erythrocyte per 100 Leukocytes

Date	Normoblasts	Megaloblasts
3/19.....	2	0
3/26.....	1	1
4/ 9.....	1	0

Form of Erythrocytes

Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
3/ 5.....	68%	30%	2%	4/ 3.....	77%	15%	8%
3/12.....	82%	18%		4/ 9.....	73%	24%	3%
3/19.....	87%	13%		4/24.....	78%	20%	2%
3/26.....	87%	13%		10/23.....	93%	6%	1%

A typical megaloblastic anemia curve with much skewness is seen which straightens up in the last tracing.

CASE 5.—*Hypoplastic Anemia of Sprue*.—A. M., a white man, a Porto Rican, aged 71, was seen on Sept. 23, 1927. The patient was profoundly affected by anemia and much less by sprue, which, while it caused a raw tongue, did not cause most of the remaining gastro-intestinal symptoms. The liver was

extremely small, there was great asthenia, much numbness and tetanoid cramping of the hands and feet. The blood pressure was 110 systolic and 80 diastolic.

In this case, the patient had fallen from his normal weight of 135 pounds (61.2 Kg.) to 113 (51.3 Kg.), but the picture of pernicious anemia was marked.

TABLE 5.—Measurements of One Hundred Erythrocytes in Case 5

Date	Diameters in Microns														Maxi- mum	Mini- mum	Mean	Median	Disper- sion
	3	4	5	6	7	8	9	10	11	12	13	14							
2/ 4.....	..	3	1	6	5	21	18	32	8	4	1	1	14	4	9.01	10.25	3.05		
2/11.....	1	..	1	4	3	21	16	36	4	10	2	2	14	3	9.43	10.2	2.90		
2/18.....	..	1	1	2	7	25	13	27	11	11	1	1	14	4	9.38	10.3	3.20		
2/25.....	1	3	..	23	20	39	6	8	12	5	9.39	10.3	3.15		
2/29.....	3	12	12	17	26	16	13	1	12	3	8.56	10.50	3.15		
3/ 6.....	2	3	12	22	39	18	2	2	12	5	8.65	9.25	2.50		
3/20.....	..	1	..	3	4	29	20	40	3	11	4	9.19	10.1	2.95		
3/27.....	3	8	33	25	20	4	2	12	6	8.71	9.45	2.2		
5/15.....	..	1	..	4	12	51	20	11	1	11	4	8.21	7.95	2.8		
6/ 6.....	1	9	41	35	13	1	11	6	8.53	8.32	2.5		
8/ 7.....	1	1	6	48	26	18	10	5	8.51	8.05	2.62		
10/ 2.....	10	52	23	14	1	11	7	8.44	7.95	2.55		

Blood Counts

Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho- nuclears	Lymphocytes	Monocytes	Eosinophils	Basophils	Plasmocytes	Metamycelo- cytes	Myelocytes
9/23	30%
12/ 6	41%	2,216,000	5,500
12/21	40%	1,728,000
1/ 4	44%
1/11	50%
1/25	42%
1/31	44%
2/ 7	57%	45	33	..	20	2	..
2/10	56%	2,048,000	5,800	25	66	1	7	..	1
2/11	55%
2/18	56%	1,952,000	4,460	62	21	..	13	..	3	1	..
2/22	63%
2/24	2,416,000	7,000
2/25	60%	58	27	4	9	1	1
2/26	63%
2/28	62%
2/29	62%	53	19	9	17	2
3/ 1	75%
3/ 2	79%
3/ 6	78%	59	22	18	1
3/ 9	75%
3/13	81%	3,248,000
3/20	75%	2,888,000	56	20	..	23	1
3/27	82%	73	8	..	19
4/ 4	3,024,000	10,000
4/10	76%	3,008,000
4/17	90%
5/ 1	3,648,000
5/15	87%	2,832,000	69	21	..	10
6/ 6	4,104,000	..	60	34	..	6
8/ 7	87%	5,848,000	18,200	67	18	1	11	1	1
10/ 2	88%	4,416,000	10,800	80	8	..	9	..	2

Form of Erythrocytes

Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
2/ 4.....	63%	37.0	..	3/20.....	90%	10%	..
2/11.....	80%	18%	2%	3/27.....	83%	17%	..
2/18.....	82%	12%	6%	5/15.....	90%	10%	..
2/25.....	74%	23%	3%	6/ 6.....	95%	5%	..
2/29.....	83%	13%	4%	8/ 7.....	90%	10%	..
3/ 6.....	90%	10%	..	10/ 2.....	93%	3%	2%

The icteric index was 13; the blood serum calcium was: total, 12.15 mg. per cent; diffuse, 6.51. The pH of the blood was 7.8 and the carbon dioxide tension in the blood, 60; the urine was normal.

He was placed on my diet, and I saw him no more until December, 1927. The favorable change in his general condition had been remarkable; he had gained 10 pounds (4.5 Kg.) in weight, but the hemoglobin was only 37 per cent and the erythrocytes 34 per cent. Despite a decided eosinophilia, no hookworm ova were found in the feces, and it is permissible to suspect that this eosinophilia was a favorable reaction to the diet prescribed. He was now urged to eat liver, which he managed to do in a desultory sort of a way until February 7, when he was placed on three vials of liver extract a day. He is now apparently cured.

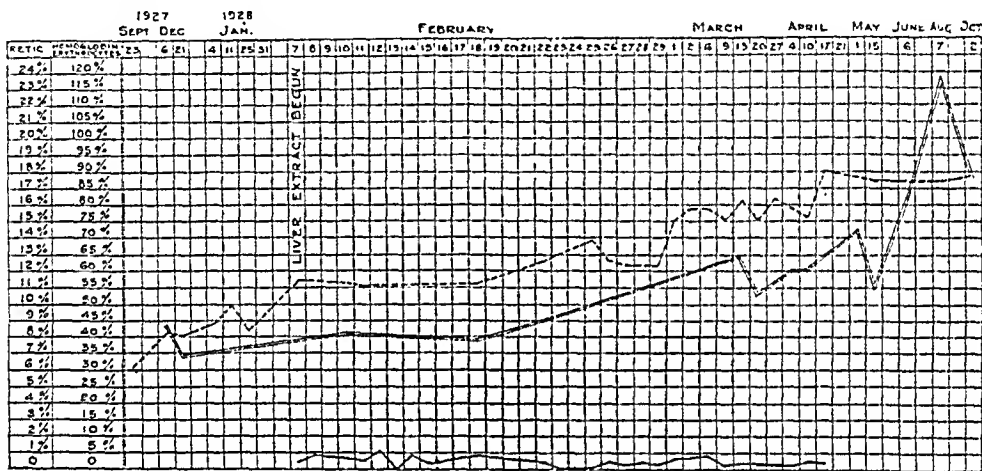


Chart 9 (case 5)

The red cells numbered 2,216,000 on the patient's admission to the hospital and gradually increased to 5,848,000 throughout nine months

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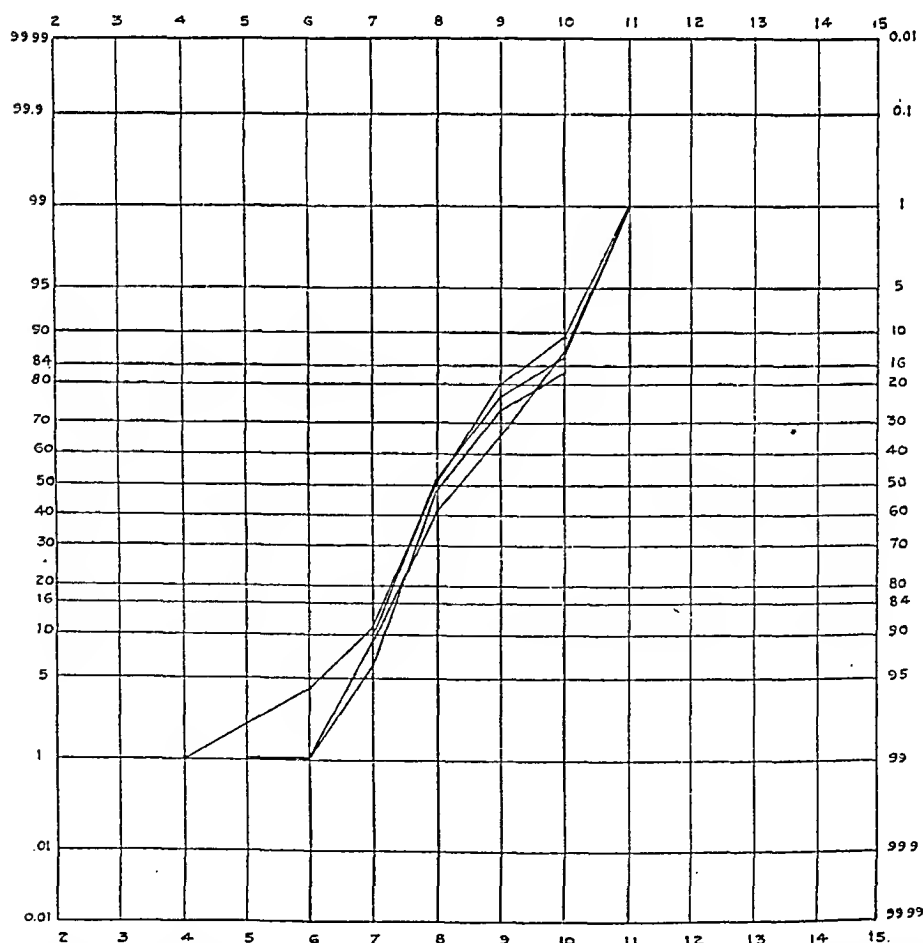
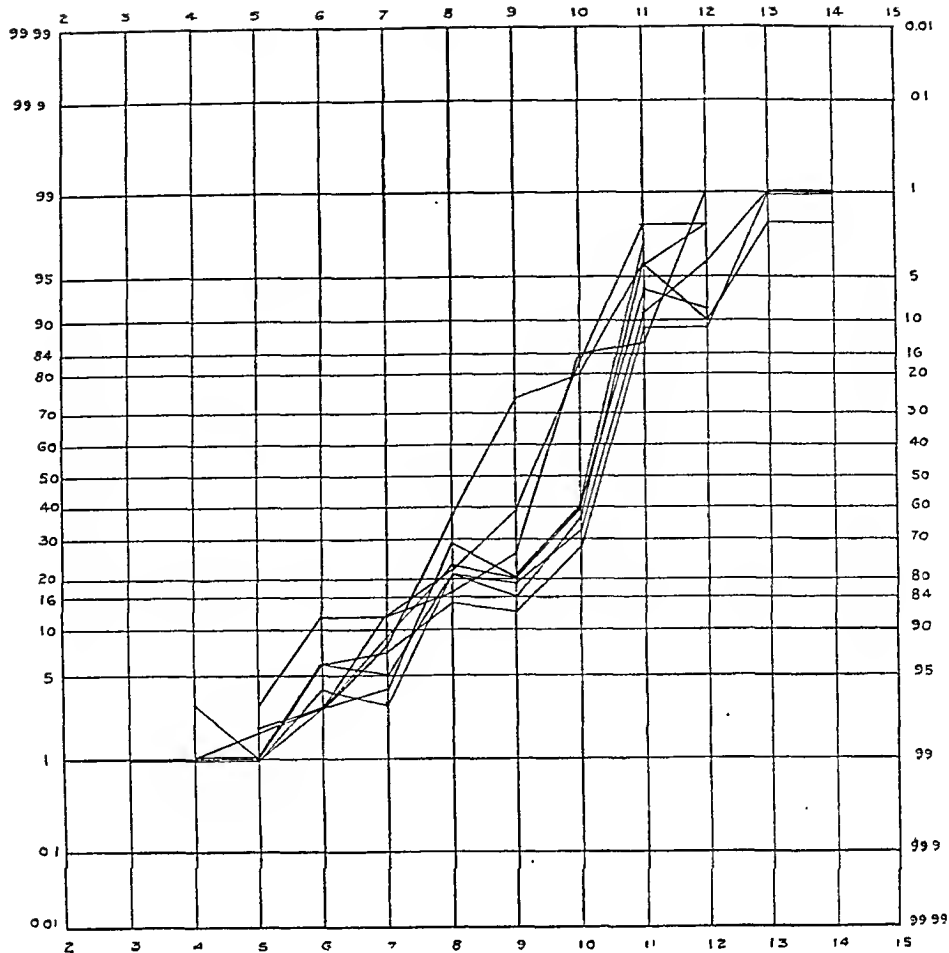


Chart 10 (case 5).—The upper chart shows curves for first period to March 27 inclusive; the lower chart, those for second period from March 27 to October 21, inclusive.

of treatment. Thirty per cent of these cells were oval or irregular on the patient's admission; only 5 per cent, on discharge. No normoblasts were ever seen.

The leukocyte count was normal toward the end, when a leukocytosis was noted. The eosinophilia throughout the course of this case was often high. At one time, marked lymphocytosis was apparent.

This case is in many respects one of the most illustrative in the series of the characteristics of the megaloblastic anemias of sprue. In the first place, the patient was an elderly man, in whom the exhaustion

TABLE 6.—*Measurements of One Hundred Erythrocytes in Case 6*

Date	Diameters in Microns						Maximum	Minimum	Median	Mean	Dispersion
	6	7	8	9	10	11					
2/ 1	8	48	40	4	9	6	7.15	7.4	2.2
2/ 7	23	57	20	8	6	6.8	6.9	2.0
2/16	8	47	39	4	1	1	11	6	7.2	7.4	2.1
2/22	5	23	60	13	9	6	7.75	7.8	2.1
2/25	3	25	65	6	1	..	10	6	7.65	7.7	1.8
4/ 5	7	53	35	4	1	..	10	6	6.95	7.39	2.2

Blood Counts											
Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho-nuclears	Lymphocytes	Monocytes	Eosinophils	Plasmocytes	Metamyelo-cytes	Myelocytes	Basophils
2/ 2	60%	4,496,000	9,600	80	18	..	1	..	1
2/ 7	56	40	..	2	..	2
2/10	66%	4,704,000
2/16	63	23	7	3	..	3	..	1
2/22	64	33	..	4	..	1	..	1
2/23	91%	4,184,000
2/25	88%	83	13	..	3	..	1
4/ 5	81%	5,832,000	11,600	78	21	..	1

Form of Erythrocytes							
Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
2/ 2	98%	2%	..	2/22	92%	8%	..
2/ 7	99%	1%	..	2/25	95%	5%	..
2/16	97%	3%	..	4/ 4	96%	4%	..

processes incidental to his nutritional defects came to the fore. That these processes enveloped and overwhelmed the blood-making organs is seen in the severe degree of megaloblastic anemia. The mean is extremely high, the median a full micron higher, and the double dispersion the highest of the series. So much for the first period, embracing five weeks.

In the second period, there was a marked reduction in the mean and in the dispersion as well as a blending of the median with the mean. This period comprised seven weeks. The persistent skewness in the first eight weeks is in striking contrast to the smoothed-out curve of the last four observations during the period of positive improvement.

CASE 6.—*Nonmegaloblastic Anemia Due to Functional Disturbance of Digestion.*—A. C., a white woman Porto Rican, aged 49, married, with three children,

was seen on Feb. 1, 1928. The patient had always enjoyed excellent health, but was suffering from the menopause and a slight hemoglobinemia due to intestinal intoxication, in turn the result of psychic disturbances suspending digestion. She was given three vials of liver extract a day from February 2 to 18.

Comment.—There was no response to liver extract. Treatment was not accompanied by clinical improvement. There was, however, a rise in the number of erythrocytes and in the hemoglobin.

The only deviation from the normal for a simple hemoglobinemia was the wide double dispersion revealed by the Price-Jones curve.

TABLE 7.—Measurements of One Hundred Erythrocytes in Case 7

Date	Diameters in Microns							Maximum	Minimum	Mean	Median	Dispersion
	4	5	6	7	8	9	10					
2/22	..	2	6	20	58	13	1	10	5	7.77	7.85	2.15
2/27	1	2	11	57	27	1	1	10	4	7.4	6.9	2.05
3/ 2	..	1	9	23	52	8	2	10	5	7.63	7.95	2.3
3/19	..	1	14	31	40	10	1	10	5	7.47	8.2	2.65
3/24	..	3	8	25	51	11	2	10	5	7.65	8.0	2.35
4/ 4	..	1	15	31	45	6	2	10	5	7.46	8.1	2.58

Blood Counts											
Date	Hemoglobin	Erythrocytes	Leukocytes	Polymorpho-nuclears	Lymphocytes	Monocytes	Eosinophils	Basophils	Plasmocytes	Metamyelo-cytes	Mycocytes
2/22	65%	4,384,000	72	27	1
2/27	61%	4,072,000	53	40	2
2/29	51%	3,528,000
3/ 2	56	40	2	1	1	..	1	..
3/10	64%	77	22	1
3/19	64%	3,736,000
3/23	64%	4,376,000	2,000
4/ 4	61%
4/17	58%

Form of Erythrocytes							
Date	Round	Oval	Irregular	Date	Round	Oval	Irregular
2/22.....	90%	9%	1%	3/10.....	90%	9%	1%
2/27.....	87%	13%	..	3/24.....	88%	11%	1%
3/ 2.....	91%	9%	..	4/ 4.....	89%	10%	1%

CASE 7.—*Nonmegaloblastic Anemia Due to Functional Disturbances of Digestion (on-coming sprue?)*.—M. H., a white woman, a Porto Rican, aged 28, married, who had two children, was seen on Feb. 22, 1928. This was a case of nutritional unbalance since childhood, with excess of fats, sweets and cereals and a constant suspension of digestion from emotive disturbances. The patient had been deprived of healthful exercise and had lived in an emotional world of her own in which every whim had been gratified by her family. The clash between her unrealizable ideals and the facts of her life for which she was unprepared had left her, consequently, a nervous wreck. In short, she had a charming personality with violently changing moods, and had never grown up. These details are submitted to illustrate the part which instability of the nervous system can play in the production of the syndrome of nutritional unbalance and later of sprue.

There had been an enormous loss of weight but as yet no definite syndrome of sprue. The blood pressure was 95 systolic and 65 diastolic. The administration of liver extract was begun on February 27 and suspended on March 28.

TABLE 8.—Price-Jones Curves in the Megaloblastic Anemias of Sprue

Case	General Average Microns Total				General Average Microns First Period				General Average Microns Second Period				
	Mean	Median	Double Dis- persion	Inclusive Dates	Mean	Median	Double Dis- persion	Inclusive Dates	Mean	Median	Double Dis- persion	Maximum Diameter	Minimum Diameter
1	8.25	8.56	2.53	2/20 to 3/13	8.20	9.14	2.87	3/22 to 7/ 9	8.27	8.22	2.41	15	2
2	8.64	8.93	2.56	2/ 3 to 2/28	8.88	9.40	2.54	3/13 to 4/27	8.40	8.66	2.58	12	5
3	7.92	8.37	2.83	3/28 to 6/ 6	7.90	8.42	2.92	7 to 25	7.73	7.80	1.80	13	3
4	8.61	9.16	2.83	3/ 5 to 4/24	8.71	9.27	2.95	10 to 26	8.00	8.50	2.90	16	2
5	8.83	9.38	2.79	2/ 4 to 2/29	9.15	10.31	3.09	3/ 6 to 10/2	8.60	8.72	2.58	14	3
Av.	8.45	8.88	2.71		8.56	9.30	2.87		8.20	8.38	2.45		
Price-Jones Curves in Nonmegaloblastic Anemias													
6	7.25	7.43	2.06	2/ 1 to 2/16	7.05	7.23	2.1	2/22 to 4/ 5	7.45	7.29	2.03	11	6
7	7.92	8.37	2.83	2/22 to 3/ 2	7.60	7.54	2.2	3/19 to 4/ 4	7.52	8.10	2.52	10	4
Av.	7.58	7.90	2.44		7.32	7.38	2.1		7.48	7.69	2.27		

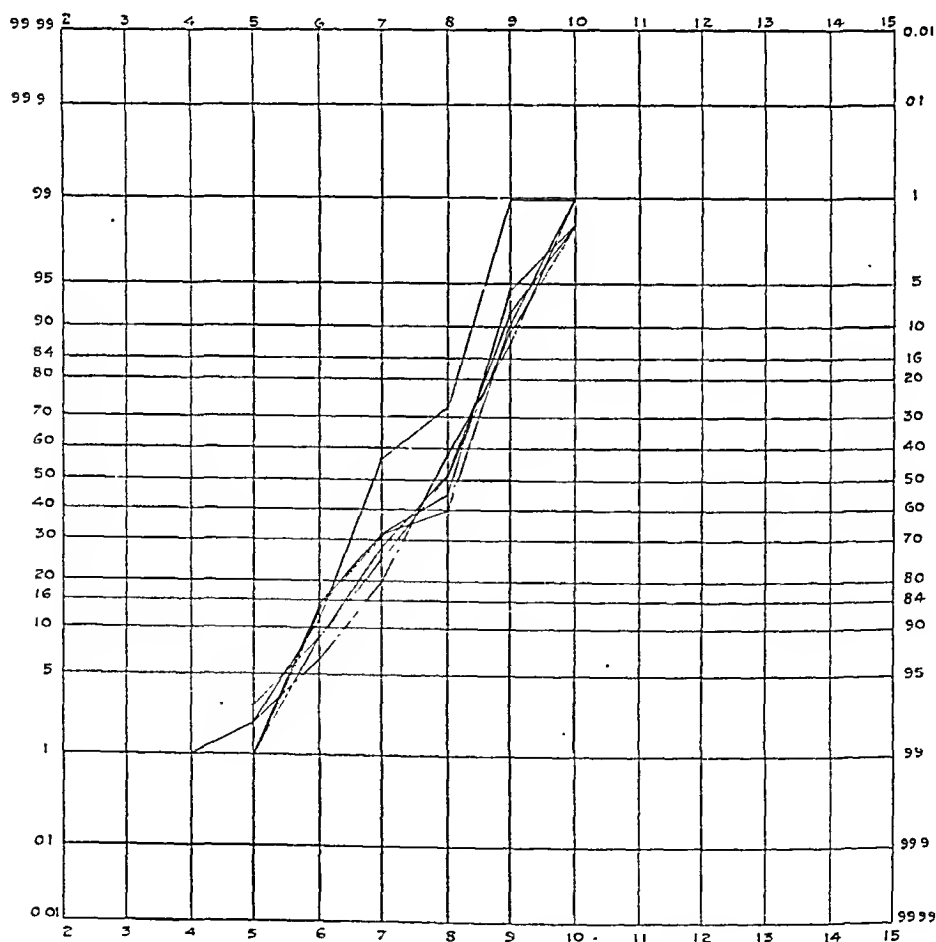


Chart 13 (case 7)

Comment.—As yet, clinical sprue cannot be definitely diagnosed, but from just such cases sprue is most frequently recruited. The case may be interpreted as one of sprue in the making, as there is a history of chronic indigestion with sharp attacks of hill diarrhea on going to the mountains.

As in the previous case, there is a wide double dispersion with an approximately normal mean and median. There is, however, in this case a definite anemia and a relatively high percentage of oval and irregular red cells.

ARTERIOSCLEROSIS IN THE YOUNG DIABETIC PATIENT *

H. CLARE SHEPARDSON, M.D.

SAN FRANCISCO

By the addition of insulin to the armamentarium for diabetic therapy, the span of life, relatively short heretofore, has been materially lengthened; consequently, a more exact knowledge of the effects produced by the long-continued presence of the disease is now obtainable.

Perhaps the most significant consequence of this increased longevity in the diabetic patient has been to make more plainly evident the interesting sequence of arteriosclerosis on diabetes. Is this a phenomenon due simply to age, or are there signs of its approach in the young? In this paper is recorded evidence bearing on this point, obtained in studying the effects diabetes of five years' duration has on persons under 40 years of age.

Arteriosclerosis is demonstrable in every patient with diabetes past middle life, according to Allen,¹ and at any age, according to others, providing the disease has been present for ten years or longer. Autopsies on fifty-two of Joslin's² patients revealed the presence of arteriosclerosis in all persons, nineteen, who had had the disease for more than five years. Wilder³ reported the observations in eighty-one autopsies on diabetic patients and noted a high incidence of arteriosclerosis. Gibb and Logan⁴ found evidence of vascular disease in sixty-three of one hundred and forty-seven necropsies on diabetic patients. The duration of the disease, however, was more than five years in only about 15 per cent of the patients.

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* This study was made possible through the courtesy of Dr. Elliott P. Joslin. Many of the patients have been mentioned elsewhere and the case numbers given are from his series. I am grateful to Dr. Morrison and Dr. Bogan of the New England Deaconess Hospital Staff, who made and interpreted the roentgen studies; to Miss Hazel Hunt for the various chemical examinations, and to Dr. Root, Dr. White and Dr. Curtis, associates of Dr. Joslin.

1. Allen, F. M.: The Dietetic Management of Diabetes, *Am. J. M. Sc.* **167**:554, 1924.

2. Joslin, Elliott P.: Arteriosclerosis and Diabetes, *Ann. Clin. Med.* **5**:1061, 1927.

3. Wilder, R. M.: Necropsy Findings in Diabetes, *South. M. J.* **19**:241, 1926.

Data of this kind, although of great importance, are meager. Furthermore, the possibility of making pathologic studies of young diabetic patients will decrease materially as their longevity increases. However, another method of study is available. Bowen and his co-workers⁵ have shown that the presence of vascular sclerosis, especially in the lower extremities, can be satisfactorily demonstrated by the roentgen ray. Although this method fails to visualize the early atheromatous changes in noncalcified arteries, positive observations, when obtained, are impressive. Bowen and Koenig⁶ recently published the results of their roentgenologic studies on 162 diabetic patients beyond the age of 40. They found demonstrable arteriosclerosis in 63 per cent. Morrison and Bogan⁷ made a similar study on 324 of Joslin's patients and found that the incidence of arteriosclerosis varied from 40 per cent in the first quinquennium of duration of the disease to 92 per cent in the fourth quinquennium. Letulle, Labbe and Heitz⁸ likewise have reported on the calcification of arteries in diabetes, as demonstrated by the roentgen ray. All of these contributions have emphasized the high incidence of arteriosclerosis in persons with diabetes, but the observations of Morrison and Bogan are especially noteworthy in calling attention to the development of a premature senility. It is the latter aspect which is of particular significance, for until it is shown that continued exposure to diabetes results in the development of arteriosclerosis, not only in the elderly patient but in the youthful one as well, the etiologic rôle of diabetes will not be proved.

The exact mechanism of the production of atheromatous changes is not well understood, but probably the most fitting explanation of the process is the "imbibition theory" originally advanced by Virchow and more recently amplified by Aschoff.⁹ While this theory may not be universally accepted, it represents the most plausible one yet proposed for diabetic arteriosclerosis. According to this theory, atheromatous

4. Gibb, W. F., Jr., and Logan, V. W.: Diabetes Mellitus, *Arch. Int. Med.* **43**:376 (March) 1929.

5. Bowen, Byron D.; Koenig, Edward C., and Viele, Anne: A Study of the Lower Extremities in Diabetes as Compared with Non-Diabetic States, from the Standpoint of X-Ray Findings with Particular Reference to the Relationship of Arteriosclerosis and Diabetes, *Bull. Buffalo Gen. Hosp.* **2**:35, 1924.

6. Bowen, Byron D., and Koenig, Edward C.: Arteriosclerosis and Diabetes, Including a Roentgenological Study of the Lower Extremities, *Bull. Buffalo Gen. Hosp.* **5**:31, 1927.

7. Morrison, L. B., and Bogan, I. K.: Bone Development in Diabetic Children: A Roentgen Study, *Am. J. M. Sc.* **174**:313, 1927.

8. Letulle, Maurice; Labbe, Marcel, and Heitz, Jean: Calcification of Arteries in Diabetes, *Arch. d. mal. du coeur* **20**:577, 1927; **18**:273, 1923.

9. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

changes might well occur in young subjects, provided, as particularly stressed by Aschoff, there is a sufficient concentration of lipids and especially of cholesterol esters in the blood stream, a condition which because of the relatively high blood cholesterol content associated with diabetes¹⁰ may obtain in young as well as in elderly diabetic patients.

The production of arteriosclerosis in animals has occupied the attention of many workers, with rather diversified and inconsistent results. The subject was reviewed by MacCollum¹¹ in 1922, at which time he expressed the opinion that experimental diets seemed the most promising means of producing arteriosclerosis in animals. Bowen⁶ briefly reviewed the literature again in December, 1927, and suggested that a disturbance in the acid-base mechanism might play a rôle. Both the dietary factor emphasized by MacCollum and the disturbance in acid-base equilibrium stressed by Bowen are generally present in either poorly treated diabetic patients or patients treated on diets high in fat, for it is in just these persons, in whom fats are improperly metabolized, that there is to be found among other things both an increased concentration of cholesterol and the more favorable medium for its esterization, a high hydrogen ion concentration.

These ideas, however, are largely speculative. There still remains much that is unknown concerning the metabolism of fats, not only in the diabetic but in the normal person, and the successful demonstration of the basic processes involved in the utilization of lipids will aid materially in clarifying the pathogenesis of atheromatous changes in the blood vessels of both normal and diseased persons.

EXPERIMENTAL WORK

In the present work, the early development rather than the mere presence of arteriosclerosis was especially investigated. In order to study the effects of diabetes on the vascular system, patients under 40 years of age were selected, thus precluding a high normal incidence of arteriosclerosis. Furthermore, it was necessary to choose persons who had been exposed to diabetes over a period of time sufficient for its influence to be manifest. A minimum duration of five years was consequently decided on.

Although the fifty cases of diabetes included in this study constitute too small a number for far-reaching conclusions, especially when there exist in this country alone possibly 1,000,000 persons who have diabetes or who will develop it before they die (Joslin¹²), it must be emphasized

10. Joslin, Elliott P.: *Treatment of Diabetes*, ed. 3, Philadelphia, Lea & Febiger, 1923.

11. MacCollum, W. G.: *Arteriosclerosis*, *Physiol. Rev.* 2:70, 1922.

12. Joslin, Elliott P.: *Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 131.

that the vast majority of diabetic patients are above the age of 40 and are consequently subject to the degeneration of advancing years. In this older group, it is impossible to separate the effects of the disease itself from the changes which are usually considered normal for persons past middle life. In attempting to ascertain the changes resulting purely from exposure to diabetes, children were, of course, the ideal subjects, but relatively few children are alive who have had the disease for five or more years. Consequently, the number was increased by including young adults, and it should be pointed out that as the intensity of diabetes decreases with the age of the patient, the disease in this group must be considered as being more severe than would be the diabetes in a group in which the average age was from twenty to thirty years older.

In this selected group of diabetic patients chosen because of an age period in which sclerotic changes are exceptional, the precise age of the person seems to bear little, if any, relation to the development of arteriosclerosis. The average age of these fifty patients was 23.4 years and the average duration of the disease was 6.93 years. Roentgenologic evidence of arteriosclerosis was demonstrated in eighteen patients, 36 per cent, of whom the average age was 25.4 years and the average duration of the disease was 7.62 years, compared with an average age of 22.3 years and an average duration of 6.55 years in the remaining group of thirty-two patients, in whom no sclerotic changes were manifest.

The youngest person in whom vascular disease was demonstrated (case 2661) was 11.5 years of age, although it should be stated that the alterations noted were not sufficiently striking to permit a positive diagnosis of arteriosclerosis. In case 2007, calcification of the peripheral vessels was plainly evident roentgenologically, in spite of the fact that the patient was only 12.9 years of age. He had had the disease for 5.8 years. In addition to diabetes, this patient had a discharging tuberculous cervical sinus, and films of the chest showed the pleural caps to be dense. He was of about normal weight. His basal metabolic rate was elevated, and his blood cholesterol was within normal limits.

The most pronounced manifestations were found in case 6359. All of the larger vessels showed marked evidence of calcification, and in addition the entire pancreas was outlined by calcium deposits. The patient was markedly underweight (43.5 per cent) and continued to be so despite a diet of 2,047 calories, 60 calories per kilogram of body weight. A history of pleurisy accompanied by hemoptysis in 1923 was obtained, but no evidence of active tuberculosis was present when she was last examined. This patient was known to have had diabetes for 5.1 years; she was 23 years of age.

For a considerable time prior to the date of investigation, most of the patients included in this study had been on a diet relatively high in carbohydrate as compared with diets before the use of insulin, but yet below what is termed today a high carbohydrate diet in the usual

TABLE 1.—*Effect of Diet on the Incidence of Arteriosclerosis*

Case Number (Joslin)	Age, Years	Duration of Diabetes Mellitus, Years	Diet			Basal Metabolism		Insulin, Units Daily	Roentgeno- graphic Evidence of Arterio- sclerosis*	
			Carbo- hydrate, Gm.	Pro- tein, Gm.	Fat, Gm.	Calories	Calories per 24 Hours			Rate
436	38.8	18.5	Variable	61	High	1,143	15—	12	+++
1469	20.8	10.0	190	60	60	1,540	1,694	1—	64	0
1609	21.0	10.3	90	60	127	1,743	2,127	28+	50	0
1616	13.8	8.3	101	73	118	1,758	1,166	16+	24	+
1714	34.4	8.8	76	84	180	2,200	1,221	15—	22	+++
1729	27.1	9.1	100	69	120	1,756	1,795	5+	34	++
1949	14.5	7.8	75	63	109	1,533	1,376	12+	34	0
1997	19.1	8.3	60	60	100	1,380	1,860	29+	35	0
2005	39.2	9.4	150	51	77	1,497	1,339	7—	10	+++
2007	12.9	5.8	141	79	94	1,726	1,572	19+	65	++
2008	36.3	7.2	100	60	90	1,450	1,413	18+	30	0
2024	18.1	10.9	41	44	83	1,087	2,023	43+	52	0
2095	34.1	7.0	115	72	148	2,080	1,421	12—	20	0
2353	15.2	6.4	65	71	109	1,525	1,359	3+	40	++
2448	24.0	6.2	100	60	100	1,540	Not done	Fever	30	+++
2528	16.7	7.5	85	75	110	1,630	1,268	1+	40	++
2560	12.4	6.5	100	64	100	1,556	1,213	6+	24	0
2615	30.8	5.9	138	81	132	2,064	1,647	6+	None	0
2617	19.8	5.7	127	73	103	1,727	1,123	16—	36	0
2661	11.5	6.3	93	57	113	1,617	1,326	20+	26	+
2675	28.8	6.0	110	69	78	1,378	1,810	6+	None	++
2680	13.7	7.7	70	69	112	1,564	1,248	5+	72	0
2708	28.8	6.0	108	68	140	1,964	2,175	21+	25	0
2757	16.1	5.4	100	75	125	1,825	1,492	14+	30	0
2784	22.3	7.0	90	78	123	1,779	1,438	4—	40	0
2811	30.5	5.6	150	90	140	2,220	1,644	4—	10	0
2847	17.5	8.5	64	71	104	1,476	1,503	13+	51	0
2932	17.4	5.0	75	60	50	990	1,685	10+	55	0
2967	34.7	5.8	60	69	157	1,929	1,438	1+	24	0
3040	15.5	5.2	183	86	133	2,273	1,759	21+	60	0
3057	22.0	5.0	91	78	138	1,918	1,752	4+	40	0
3062	37.5	5.5	88	69	124	1,744	1,411	2+	50	++
3078	17.3	5.0	96	64	104	1,576	1,270	3—	50	0
3147	14.0	4.8	78	78	117	1,677	1,444	10+	45	0
3175	37.8	5.0	131	79	108	1,812	1,505	9+	40	++
3262	12.3	5.2	103	68	140	1,944	1,116	Normal	18	0
3332	22.0	5.0	104	79	192	2,460	Not done	7	0
3353	15.8	5.3	80	66	110	1,574	1,628	30+	45	0
3620	16.4	5.3	78	53	94	1,370	1,626	37+	45	+++
3729	29.5	5.0	61	56	126	1,602	1,299	8+	28	0
3778	14.2	8.0	60	60	100	1,380	1,283	7+	39	0
3852	36.9	8.6	88	62	118	1,662	1,208	7—	None	0
4111	38.8	6.5	88	83	117	1,737	1,436	2—	8	0
4232	20.5	6.4	86	69	118	1,682	1,543	10+	35	+++
4743	19.3	4.7	75	60	100	1,440	1,419	2—	15	0
5433	22.0	5.5	118	78	142	2,068	1,733	4+	45	++
5978	35.2	5.5	109	62	95	1,539	1,274	13+	20	0
6359	23.1	5.1	92	71	155	2,047	1,120	4—	35	+++
6416	13.9	5.3	80	80	141	1,909	1,776	39+	49	0
6717	37.5	12.1	133	55	56	1,256	1,321	5+	20	+++
Average	23.4	6.98	97.8	68.2	114.6	1,699.2	1,488.5		35	

* In this and the subsequent tables, +++ indicates marked; ++, trace; +, questionable; 0, none.

sense. The proportions of carbohydrate, protein and fat contained in the diets of the various subjects are given in table 1. These data are summarized in table 6, which shows the average diet of the group in which roentgenologic evidence of arteriosclerosis existed to be carbohydrate, 102 Gm.; protein, 67 Gm.; fat, 112 Gm.; calories 1,684, as

compared with the average diet of carbohydrate, 95 Gm.; protein, 69. Gm.; fat, 117 Gm.; calories, 1,709, of those patients in whom no abnormal vascular changes were found. It is interesting that the diets of the two groups were almost identical, there being a variation of only 7 Gm. of carbohydrate, 2 Gm. of protein and 5 Gm. of fat. The proportion of food intake to basal caloric requirement was slightly higher in the group in which sclerotic changes were manifest, but this variation is so small as to be of little consequence. Perhaps the most interesting feature brought out by an analysis of the diets is the fact that the carbohydrate intake of the entire group was much higher than that permitted prior to the discovery of insulin. This is of considerable importance, for, as Joslin has suggested, the relatively high carbohydrate content of the diet (made possible by insulin) may definitely interfere with the development of vascular disease. As the quantity of carbohydrate oxidized seems to be of greater significance in maintaining a fairly normal blood lipid level than is the fat administered in the diet, the better utilization of carbohydrate permitted by insulin may play an extremely important rôle in lowering the incidence of arteriosclerosis, even in long-standing cases of diabetes.

Heretofore the blood lipids in diabetes have tended to be well above normal, and various investigators (Gray,¹³ Blix¹⁴) have shown that the percentage of fat in the blood rises with the severity of the disease. In fact, Rabinowitch,¹⁵ after analyzing data obtained in 385 patients, found the plasma cholesterol a reliable index of the true progress of the diabetic patient. However, it probably can be assumed that the blood lipid level will remain relatively low, even in severe diabetes, provided sufficient insulin is administered to metabolize properly the carbohydrate element of the diet. Furthermore, there is a possibility that insulin has a direct influence on fat metabolism. Consequently, there is every reason to believe that Joslin's suggestion regarding the effects of an increased utilization of carbohydrate on vascular disease is correct. The incidence of arteriosclerosis in the present series, which is considerably lower than former writings would have led one to expect, not only seems to confirm this, but suggests further that already within the first decade of the Banting era the high carbohydrate allowance has favorably retarded the development of arteriosclerosis.

As has been repeatedly suggested in the more recent literature, the height of the blood sugar is probably not as accurate an indication of

13. Gray, H.: Lipoids in 1000 Diabetic Bloods with Special Regard to Prognosis, *Am. J. M. Sc.* **168**:33, 1924.

14. Blix, Gunnar: Studies on Diabetic Lipemia, *Acta med. Scandinav.* **64**:142, 1926.

15. Rabinowitch, I. M.: The Cholesterol Content of Blood Plasma in Diabetes Mellitus, *Arch. Int. Med.* **43**:363 (March) 1929.

the severity of diabetes as is the evidence of impaired fat metabolism. This is further emphasized by the data given in table 2, in which are recorded the highest and lowest amounts of blood sugar obtained in the various cases. Consequently, it is not surprising to find that the extent of the glycemia has little influence on the development of arterio-

TABLE 2.—*Effect of Blood Sugar Range on the Incidence of Arteriosclerosis*

Case Number (Joslin)	Age, Years	Duration of Diabetes Mellitus, Years	Blood Sugar Range	Roentgenologic Evidence of Arteriosclerosis
430.....	33.8	18.5	0.09 - 0.27	+++
1714.....	34.4	8.8	0.08 - 0.26	+++
2005.....	39.2	9.4	0.18 - 0.28	+++
2448.....	24.0	6.2	0.05 - 0.50	+++
3620.....	16.4	5.3	0.03 - 0.54	+++
4232.....	20.5	6.4	0.05 - 0.49	+++
6359.....	23.1	5.1	0.13 - 0.33	+++
6717.....	37.5	12.1	0.09 - 0.22	+++
1616.....	13.8	8.3	0.04 - 0.37	++
1729.....	27.1	9.1	0.04 - 0.49	++
2007.....	12.9	5.8	0.09 - 0.29	++
2353.....	15.2	6.4	0.09 - 0.39	++
2528.....	16.7	7.5	0.05 - 0.31	++
2675.....	28.8	6.0	0.04 - 0.25	++
3062.....	37.5	5.5	0.06 - 0.44	++
3175.....	37.8	5.0	0.15 - 0.33	++
5433.....	22.0	5.5	0.06 - 0.27	++
2661.....	11.5	6.3	0.03 - 0.32	+
1469.....	20.8	10.0	0.038 - 0.35	0
1609.....	21.0	10.3	0.07 - 0.56	0
1949.....	14.5	7.8	0.08 - 0.22	0
1997.....	19.1	8.3	0.13 - 0.36	0
2008.....	26.3	7.2	0.04 - 0.29	0
2021.....	18.1	10.9	0.13 - 0.46	0
2095.....	34.1	7.0	0.05 - 0.22	0
2560.....	12.4	6.5	0.04 - 0.33	0
2615.....	30.8	5.9	0.09 - 0.21	0
2617.....	19.8	5.7	0.06 - 0.33	0
2680.....	13.7	7.7	0.07 - 0.48	0
2708.....	28.8	6.0	0.07 - 0.19	0
2757.....	16.1	5.4	0.04 - 0.35	0
2784.....	22.3	7.0	0.10 - 0.24	0
2811.....	30.5	5.6	0.08 - 0.28	0
2847.....	17.5	8.5	0.12 - 0.39	0
2962.....	17.4	5.0	0.08 - 0.32	0
2967.....	34.7	5.8	0.08 - 0.40	0
3040.....	15.5	5.2	0.047 - 0.56	0
3057.....	22.0	5.0	0.09 - 0.31	0
3078.....	17.3	5.0	0.08 - 0.36	0
3147.....	14.0	4.8	0.06 - 0.52	0
3262.....	12.3	5.2	0.06 - 0.32	0
3332.....	22.0	5.0	0.08 - 0.29	0
3353.....	15.8	5.3	0.11 - 1.10	0
3729.....	29.5	5.0	0.07 - 0.36	0
3778.....	14.2	8.0	0.05 - 0.31	0
3852.....	36.9	8.6	0.09 - 0.26	0
4111.....	38.8	6.5	0.09 - 0.26	0
4743.....	19.3	4.7	0.08 - 0.27	0
5978.....	35.2	5.5	0.08 - 0.29	0
6416.....	13.9	5.3	0.13 - 0.28	0

sclerosis. In several of the patients with no demonstrable sclerosis the blood sugar ranged between rather high limits (cases 1609, 3040, 3353), while in many of those showing definite arterial calcification, blood sugar determinations made on numerous occasions failed to reveal more than a nominal elevation.

The data recorded in table 3 indicate that neither essential hypertension nor cardiorenal vascular disease plays an important rôle in the development of the arteriosclerosis associated with diabetes. Of the

four cases (the patient in case 1616 was in coma when the determination was made) in which evidence of nitrogen retention existed, there were sclerotic vessels in three, and in only one of these an impaired kidney function. The latter patient (case 2005), aged 39.5 years, had had diabetes for a least 9.4 years. All of the cardinal signs of cardiorenal vascular disease were present; the blood pressure was elevated, the phenolphthalein excretion was low, and there was definite nitrogen retention as well as fixation of specific gravity in the urine. It is, of course, impossible to state what relation diabetes had to the rather extensive arteriosclerosis this patient exhibited. Four others had moderately elevated blood pressures without evidence of renal pathology: case 2675, blood pressure, 148 systolic and 100 diastolic with arteriosclerosis; case 3332, blood pressure, 140 systolic and 90 diastolic; case 3778, blood pressure, 130 systolic and 80 diastolic; case 3852, blood pressure, 156 systolic and 90 diastolic, in which no arteriosclerosis was demonstrated.

It is interesting to note that of the eighteen patients who showed sclerotic changes, four (cases 1007, 2448, 4232 and 6359) had or were known to have had tuberculosis, while of the group in which no sclerosis was evident, only one showed clinical or roentgenologic evidence of a tuberculous infection. Possibly the alteration in calcium metabolism and the effect on blood cholesterol which tuberculosis has been shown to cause¹⁶ are contributing factors in the development of arteriosclerosis when tuberculosis is associated with diabetes. This association, however, cannot be of basic importance, since the great majority of diabetic patients in whom arterial disease can be demonstrated are not tuberculous.

In a group of patients such as this, all of whom were hospital patients, complicating pathologic conditions were to be expected. This incidence, however, was remarkably low. In addition to the patients mentioned, such complicating factors were found in but seven cases, in none of which arterial calcification could be demonstrated. A girl, (case 1469), aged 20, was clinically a pituitary type, with a height of 69 inches (172.5 cm.) and a weight 12 per cent above the ideal. In case 2615, the patient in addition to a nontoxic multinodular colloid goiter, had minor changes in the blood vessels of the fundus of the left eye without other evidence of kidney diseases. In case 2708, the patient had orthostatic albuminuria. The latter case is of interest, because clinically the patient was thought to have definite sclerosis of the radial arteries; apparently calcification had not taken place, since this impression was not confirmed by the roentgen ray. In case 3078,

16. Gavrila, I., and Vior: La cholesterinemie chez les tuberculeux, *Compt. rend. Soc. de biol.* 97:769, 1927.

the patient had a small nontoxic adolescent goiter. In case 3729, the patient had carotinemia, xanthosis and fine granular casts in the urine (the latter observations were obtained while the patient was still in a state of acidosis following coma); there was no nitrogen retention, and her phthalein excretion was 55 per cent. In case 3778, the patient had clinical and roentgenologic evidence of early tuberculosis (she was 15 per cent underweight, and her radial arteries were definitely palpable although no calcification was revealed by the roentgen ray). In case 6416 the patient was somewhat anemic and had occasional enuresis and some involuntary diuresis, but no other evidence of kidney disease.

COMMENT

This work has definitely established the fact that vascular disease occurs with greater frequency and at a much earlier age in diabetic patients (at least in those who have been subjected to the influence of the disease over a period of five or more years) than in normal persons. But in order to determine the nature of the injurious effects of diabetes on the vascular system, it is necessary to analyze the many variable factors found to exist in the group of patients studied. Joslin has pointed out that the longer the disease continues, the greater is the probability that arterial changes are present, regardless of the age of the person. This, however, is not the only factor, and in the present group there are a sufficient number of exceptions to this statement to prohibit its complete acceptance. Certainly, exposure to the disease over a long period must be a contributing factor in the development of arterial changes, since the longer the causative agent is allowed to operate, the more surely will pathologic changes result. But comparison of the patient in case 1609, aged 21, who had had the disease for 10.3 years without evidence of arteriosclerosis, with the one in case 4232, aged 20.5 years, who had had the disease for only 6.4 years and in whom marked vascular disease existed, forbids the assumption that duration of the disease by itself constitutes a fundamental etiologic condition.

Likewise, the severity of the disease would be expected to play an important part in the development of vascular pathologic changes. This, however, is an intangible factor, difficult of measurement, which can be but inaccurately estimated. Most of the patients of this series in whom sclerosis was roentgenologically evident impressed one clinically as having diabetes in a more severe form than those in whom no such changes were found. Numerous exceptions, however, occur: The patient in case 436 can hardly be considered as having a severe case of diabetes, and table 6, showing the averages for the group, indicates that the cases of arteriosclerosis were even less severe than those in patients in whom sclerotic alterations were not apparent. Further-

more, analysis of the data obtained for the individual cases fail to support the assumption that the severity of the disease is of primary importance. For example, in the patient in case 3353, aged 15.8 years, who had had the disease for 5.3 years and required 45 units of insulin to metabolize a diet consisting of 80 Gm. of carbohydrate, 66 Gm. of protein and 110 Gm. of fat, or 1,574 calories, no roentgenologic evidence of vascular disease was obtained; whereas, a patient (case 3620), aged 16.4 years, similar in all respects, who had been exposed to diabetes at least 5.3 years and required 45 units of insulin to metabolize a diet of 78 Gm. of carbohydrate, 53 Gm. of protein and 94 Gm. of fat, or 1,370 calories, showed marked evidence of arteriosclerosis. Then too, interestingly enough, of the eighteen patients showing sclerotic alterations in their vessels, eight, or 44 per cent, had hereditary diabetes usually considered a mild form. Probably, therefore, as the results obtained in this investigation seem to indicate, the severity of the diabetes, especially if adequately controlled by treatment, is of but slight importance in the premature development of senility.

Another factor which probably has some influence on the development of vascular disease, but which is not of fundamental importance, is the existence of complicating conditions. Certain members of this group had evidence of slight pathologic changes in the kidney, others had evidence of endocrine or cardiac disease or gastro-intestinal disturbances, but these complications were not sufficiently consistent in those who had arteriosclerosis to warrant their being given serious consideration. Also, in several of the patients who were obviously sclerotic, no associated pathologic condition could be demonstrated. Consequently, with the possible exception of tuberculosis, pathologic conditions associated with diabetes cannot be considered to be more than incidental factors in the development of arteriosclerosis.

Diabetes mellitus is a disease that produces marked alterations in metabolism. It, therefore, verges on the prophetic to attempt to assign the chief rôle in the premature development of arteriosclerosis to any one of the numerous and variable abnormal metabolic disturbances. More and more, however, physicians are beginning to realize that in diabetes mellitus perhaps the greatest variation from the normal occurs in the metabolism of fats. A few years ago, Joslin¹⁷ called attention to the fact that a group of diabetic patients whose condition he considered mild had an average plasma cholesterol of 260 mg. per hundred cubic centimeters of blood, while a group classed by him as moderately diabetic had an average plasma cholesterol of 300 mg., and his patients with severe cases had an enormous elevation of plasma cholesterol, to an average of 510 mg. In contrast to this, the average blood chole-

17. Joslin (footnote 12, p. 239).

sterol values obtained for the entire group covered by this investigation were found to be only 222.9 mg. per hundred cubic centimeters (table 4). If one assumes that the observations of earlier clinicians, supported as they were by the investigations of Joslin and others, are

TABLE 3.—*Relation of Kidney Function to the Incidence of Arteriosclerosis*

Case No. (Joslin)	Age, Years	Duration of Diabetes Mellitus, Years	Non- protein Nitrogen, Mg. per 100 Cc. of Blood	Phenol- protein phthalein, Total 24 Hour Excre- tion	Two Hour Renal Function Range of Specific Gravity	Blood Pressure	Roent- genologic Evidence of Arterio- sclerosis
436	38.8	18.5	0.30	40	Not done	112 / 80	+++
1714	34.4	8.8	0.31	48	Not done	102 / 65	+++
2005	39.2	9.4	0.65	10	1.009-1.016	109 / 108	+++
2448	24.0	6.2	0.24	Not done	Not done	80 / 60	+++
3620	16.4	5.3	0.27	54	1.004-1.006	110 / 80	+++
4232	20.5	6.4	0.37	35	Not done	120 / 80	+++
6359	23.1	5.1	0.29	43	1.018-1.022	100 / 80	+++
6717	37.5	12.1	0.32	45	1.014-1.030	145 / 90	+++
1616	13.8	8.3	0.72*	48	1.006-1.022	110 / 80	++
1729	27.1	9.1	0.37	51	1.016-1.028	110 / 60	++
2007	12.9	5.8	0.34	22	1.007-1.027	110 / 50	++
2353	15.2	6.4	0.32	42	1.005-1.031	104 / 80	++
2528	16.7	7.5	0.26	33	1.012-1.034	80 / —	++
2675	28.8	6.0	0.24	28	1.014-1.028	148 / 100	++
3062	37.5	5.5	0.23	34	1.014-1.036	130 / 80	++
3175	37.8	5.0	0.32	Not done	1.010-1.024	84 / 40	++
5433	22.0	5.5	0.43	40	1.018-1.035	120 / 80	++
2661	11.5	6.3	0.24	68	1.012-1.024	90 / 60	+
1469	20.8	10.0	0.28	42	1.024-1.036	100 / 70	0
1609	21.0	10.3	0.29	45	1.014-1.035	130 / 80	0
1949	14.5	7.8	0.28	35	1.012-1.020	110 / 60	0
1997	19.1	8.3	0.22	54	1.019-1.038	115 / 72	0
2008	36.3	7.2	0.32	62	1.006-1.013	100 / 80	0
2024	18.1	10.9	0.36	71	1.023-1.037	100 / 60	0
2095	34.1	7.0	0.30	27	1.010-1.026	115 / 70	0
2560	12.4	6.5	0.38	63	1.016-1.032	114 / 76	0
2615	30.8	5.9	0.33	56	1.016-1.030	104 / 65	0
2617	19.8	5.7	Not done	26	1.006-1.022	106 / 76	0
2680	13.7	7.7	0.31	41	1.006-1.024	90 / 60	0
2708	23.8	6.0	0.33	44	1.012-1.030	128 / 82	0
2757	16.1	5.4	0.21	60	1.010-1.036	110 / 80	0
2784	22.3	7.0	0.32	54	1.006-1.028	120 / 80	0
2811	30.5	5.6	0.51	65	1.004-1.024	120 / 80	0
2847	17.5	8.5	6.25	36	1.016-1.034	128 / 86	0
2962	17.4	5.0	0.53	61	1.028-1.042	100 / 80	0
2967	34.7	5.8	0.32	58	1.021-1.031	100 / 50	0
3040	15.5	5.2	0.37	Not done	Not done	120 / 80	0
3057	22.0	5.0	0.33	32	1.017-1.032	110 / 80	0
3078	17.3	5.0	0.25	50	1.009-1.015	100 / 60	0
3147	14.0	4.8	0.30	65	1.018-1.030	120 / 80	0
3262	12.3	5.2	0.34	Not done	1.020-1.031	94 / 54	0
3332	22.0	5.0	0.36	53	Not done	140 / 90	0
3353	15.8	5.3	0.37	35	Not done	110 / 80	0
3729	29.5	5.0	6.54	55	1.025-1.034	102 / 70	0
3778	14.2	8.0	0.29	45	1.010-1.032	130 / 80	0
3852	26.9	8.6	0.28	58	1.008-1.026	156 / 90	0
4111	38.8	6.5	0.34	50	1.008-1.032	118 / 68	0
4743	19.3	4.7	Not done	53	1.005-1.017	106 / 74	0
5978	35.2	5.5	0.52	65	1.016-1.034	106 / 80	0
6416	13.9	5.3	0.27	38	1.014-1.026	92 / 60	0
Average	23.4	6.93	0.33	46.5			

* The patient was in a state of coma when the count was taken.

well founded and that exposure to diabetes over a period of from five to ten years heretofore almost invariably resulted in vascular sclerosis, one is confronted with a striking parallelism between the reduction in average values of blood cholesterol and the reduction in the incidence of arteriosclerosis. This parallelism seems to support indirectly

Aschoff's theory of the development of atheromatous changes, a theory which many of those interested in diabetes have felt was probably correct so far as sclerotic changes associated with diabetes are concerned. Because of the greater quantities of carbohydrates oxidized in the pres-

TABLE 4.—*Effect of Blood Cholesterol on the Incidence of Arteriosclerosis*

Case Number (Joslin)	Age, Years	Duration of Diabetes Mellitus, Years	Blood Cholesterol, Mg. per 100 Cc.	Roent- genologic Evidence of Arterio- sclerosis
433.....	38.8	18.5	157	+++
1714.....	34.4	8.8	271	+++
2005.....	39.2	9.4	416	+++
2448.....	24.0	6.2	90	+++
3620.....	16.4	5.3	185*	+++
4232.....	20.5	6.4	275	+++
6359.....	23.1	5.1	102	+++
6717.....	37.5	12.1	196	+++
1616.....	13.8	8.3	222	++
1729.....	27.1	9.1	170	++
2007.....	12.9	5.8	165	++
2353.....	15.2	6.4	207	++
2528.....	16.7	7.5	312	++
2675.....	28.8	6.0	300	++
3062.....	37.5	5.5	188	++
3175.....	37.8	5.0	242	++
5433.....	22.0	5.5	200	++
2361.....	11.5	6.3	240	+
1469.....	20.8	10.0	232	0
1609.....	21.0	10.3	220	0
1949.....	14.5	7.8	183	0
1997.....	19.1	8.3	175	0
2003.....	36.3	7.2	225	0
2024.....	18.1	0.9	270	0
2095.....	34.1	7.0	192	0
2569.....	12.4	6.5	267	0
2615.....	30.8	5.9	207	0
2617.....	19.8	5.7	298	0
2630.....	13.7	7.7	147	0
2708.....	28.8	6.0	186	0
2757.....	16.1	5.4	327	0
2784.....	22.3	7.0	270	0
2811.....	30.5	5.6	210	0
2847.....	17.5	8.5	150	0
2962.....	17.4	5.0	330	0
2937.....	34.7	5.8	205	0
3040.....	15.5	5.2	270	0
3057.....	22.0	5.0	214	0
3078.....	17.3	5.0	164	0
3147.....	14.0	4.8	195	0
3262.....	12.3	5.2	283	0
3332.....	22.0	5.0	187	0
3353.....	15.8	5.3	200	0
3729.....	29.5	5.0	155	0
3778.....	14.2	8.0	347	0
3852.....	36.9	8.6	276	0
4111.....	38.8	6.5	247	0
4743.....	19.3	4.7	266	0
5978.....	35.2	5.5	175	0
6116.....	13.9	5.3	138	0
Average.....	23.4	6.93	222.0	

* Taken during posteoma hyperglycemia. To be repeated.

ent "Banting epoch" of diabetic therapy, the blood lipids have not continued to be as high as formerly. Consequently, the various factors enumerated by Aschoff, MacCollum, Bowen and others as being necessary for the development of atheromatous and sclerotic changes have been in part eliminated. No longer does one find in the diabetic patient, regardless of the duration of the disease, a markedly increased

concentration of cholesterol, or the high hydrogen ion concentration so necessary for the proper esterization of that substance. This is apparently one of the outstanding achievements of insulin, for while it is certain that the severity of diabetes has not changed, the intensity of

TABLE 5.—*Actual and Ideal Weights; Incidence of Arteriosclerosis*

Case No. (Joslin)	Age, Years	Duration of Diabetes Mellitus, Years	Height, Inches	Weight, Pounds	Normal Weight, Pounds	Percentage Above or Below Normal Weight	Roent- genologic Evidence of Arterio- sclerosis
436	38.8	18.5	64 $\frac{3}{4}$	133 $\frac{1}{2}$	139	3.0—	+++
1714	34.4	8.8	66 $\frac{1}{2}$	119 $\frac{1}{2}$	148	18.9—	+++
2005	39.2	9.4	63 $\frac{1}{4}$	154 $\frac{3}{4}$	132	17.4+	+++
2448	24.0	6.2	67 $\frac{3}{4}$	100	145	31.0—	+++
3620	16.4	5.3	55	54	70	22.8—	+++
4232	20.5	6.4	61 $\frac{1}{2}$	124 $\frac{1}{2}$	126	0.9—	+++
6359	23.1	5.1	63	74	131	43.5—	+++
6717	37.5	12.1	68 $\frac{1}{2}$	107	144	25.7—	+++
1616	13.8	8.3	51 $\frac{3}{4}$	62	70	11.4—	++
1729	27.1	9.1	68	152 $\frac{1}{2}$	151	1.3+	++
2007	12.9	5.8	60 $\frac{1}{2}$	91 $\frac{1}{4}$	95	3.1—	++
2353	15.2	6.4	59 $\frac{1}{2}$	106 $\frac{3}{4}$	102	4.9+	++
2528	16.7	7.5	61 $\frac{3}{4}$	93 $\frac{1}{2}$	115	18.2—	++
2675	28.8	6.0	63 $\frac{1}{2}$	211 $\frac{3}{4}$	126	68.2+	++
3062	37.5	5.5	65 $\frac{1}{2}$	139 $\frac{1}{4}$	144	3.4—	++
3175	37.8	5.0	69 $\frac{1}{2}$	113 $\frac{1}{2}$	164	30.4—	++
5433	22.0	5.5	71	137	159	13.8—	++
2661	11.5	6.3	52 $\frac{3}{4}$	66	66	0	+
1469	20.8	10.0	69	159 $\frac{3}{4}$	142	12.0+	0
1609	21.0	10.3	66 $\frac{1}{4}$	141	139	1.5+	0
1949	14.5	7.8	54 $\frac{1}{4}$	89	82	8.5+	0
1997	19.1	8.3	63 $\frac{3}{4}$	133 $\frac{3}{4}$	122	9.8+	0
2008	36.3	7.2	63	98	136	27.9—	0
2024	18.1	10.9	62 $\frac{1}{2}$	112	125	10.4—	0
2095	34.1	7.0	69	142 $\frac{3}{4}$	159	10.0—	0
2560	12.4	6.5	56 $\frac{1}{4}$	70	78	10.2—	0
2615	30.8	5.9	70	131 $\frac{3}{4}$	164	19.5—	0
2617	19.8	5.7	61 $\frac{1}{2}$	87	117	25.6—	0
2680	13.7	7.7	56 $\frac{3}{4}$	81 $\frac{1}{2}$	82	0	0
2708	28.8	6.0	70 $\frac{3}{4}$	168 $\frac{1}{2}$	163	3.0+	0
2757	16.1	5.4	63 $\frac{1}{2}$	94	115	18.2—	0
2784	22.3	7.0	67 $\frac{3}{4}$	115	145	20.7	0
2811	30.5	5.6	72 $\frac{1}{4}$	154	176	12.5—	0
2847	17.5	8.5	62	108 $\frac{1}{4}$	118	8.4—	0
2962	17.4	5.0	62 $\frac{1}{2}$	151	118	27.9+	0
2937	34.7	5.8	68 $\frac{1}{2}$	118	156	24.3—	0
3040	15.5	5.2	65 $\frac{1}{4}$	129 $\frac{1}{2}$	124	4.0+	0
3057	22.0	5.0	73 $\frac{1}{2}$	141	171	17.5—	0
3078	17.3	5.0	63 $\frac{1}{2}$	103	120	14.1—	0
3147	14.0	4.8	63 $\frac{1}{2}$	100	114	12.2—	0
3262	12.3	5.2	57 $\frac{1}{2}$	65 $\frac{1}{2}$	83	20.4—	0
3332	22.0	5.0	70	150	154	2.5—	0
3353	15.8	5.3	59 $\frac{3}{8}$	86	91	5.5—	0
3729	29.5	5.0	60 $\frac{1}{2}$	93 $\frac{3}{4}$	119	21.0—	0
3778	14.2	8.0	58	79	93	15.0—	0
3852	36.9	8.6	63 $\frac{3}{4}$	121 $\frac{1}{2}$	133	8.2—	0
4111	38.8	6.5	67 $\frac{1}{2}$	135 $\frac{1}{4}$	153	11.1—	0
4743	19.3	4.7	62	140	118	10.1+	0
5978	35.2	5.5	63 $\frac{3}{4}$	102 $\frac{1}{4}$	133	22.5—	0
6416	13.9	5.3	59 $\frac{1}{4}$	86	91	5.5—	0
Average	23.4	6.93	63.6	114.5	125.2		

its effects on the human body have been definitely altered. Therefore, such a striking parallelism as that existing between the average reduction of blood cholesterol and the lowered incidence of arteriosclerosis can hardly be ignored. Indeed, it becomes necessary to assume that this parallelism is of definite significance and that the disturbance in fat metabolism resulting from the presence of either untreated or improperly treated diabetes is the pathogenic agent in the formation of arteriosclerosis.

Newburgh¹⁸ has recently called attention to the importance of the total caloric intake as the causative agent of the increased lipemia found in diabetes. While the assertion that this is the sole factor in the development of hypercholesteremia is open to question, the fact remains that the patients of this group—in whom, as compared to the patients of previous diabetic epochs, a definitely lowered incidence of arteriosclerosis has been shown to exist—have not only been on diets containing a relatively high proportion of carbohydrate, but, of probably equal importance, as Allen and Joslin pointed out years ago, they have been slightly undernourished. Table 5 indicates that 70 per cent were actually underweight, and of the eleven persons found to be above their ideal weight, five were within the normal variation of 5 per cent. Consequently, the results of this study seem to indicate that

TABLE 6.—*Averages of Fifty Cases*

	Number of Cases					Diet				Basal Metabolism						
	Male	Female	Age, Years	Duration of Diabetes Mellitus, Years	Carbohydrate	Protein	Fat	Calories	Calories per 24 Hours	Rate, per Cent	Insulin, Units Daily	Blood Cholesterol, Mg. per 100 Cc.	Blood Sugar Range, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc. Blood	Phenolphthalein, Total Two Hour Excretion	
Arteriosclerosis Present.....	18	10	8	25.4	7.62	102	67	112	1,684	1,427	5+	34	218.7	0.075 0.35	34.5	40.0
Absent.....	32	18	14	22.3	6.55	95	69	117	1,706	1,522	10+	26	225.3	0.077 0.36	32.0	49.9
*Average for entire group.....	50	28	22	23.4	6.93	98	68	115	1,699	1,488	35	222.9	32.9	46.5

continued use of such diets, together with the addition of sufficient insulin to permit the proper utilization, not only of the increased carbohydrate increment, but of the total food intake as well, will still further retard the development of arteriosclerosis and eventually result in an incidence but slightly greater than that to be found in normal persons.

SUMMARY AND CONCLUSIONS

1. A group of fifty diabetic patients who had had the disease for at least five years and who were under 40 years of age was studied to determine the incidence of arteriosclerosis as evidenced by the roentgen ray. The pathogenesis of vascular disease occurring so commonly in diabetes was also investigated.

2. The average age of the entire group was 23.4 years, and the average duration of the disease was 6.9 years.

18. Newburgh, L. H.: The Dietetic Treatment of Diabetes Mellitus, *Ann. Int. Med.* 2:645, 1929.

3. Eighteen cases, or 36 per cent, gave roentgenologic evidence of vascular sclerosis.

4. The data obtained in this investigation are summarized in six tables.

5. Neither the severity of the disease nor the presence of associated pathologic changes, with the possible exception of tuberculosis, can be considered as a pathogenic factor in the development of arteriosclerosis in diabetes. The duration of the disease is important only because the causative factor must act over a reasonable period of time before its effects are manifest.

6. The average values of blood cholesterol found in this group were markedly lower than those heretofore obtained, and, paralleling the reduction of lipemia, the incidence of arteriosclerosis was found to be greatly reduced.

7. The definite lessening of the intensity of the damage resulting from prolonged exposure to diabetes, consequent on the addition of insulin to diabetic therapy, has resulted in a marked lowering of the average blood lipid content. The parallel reduction in the incidence of arteriosclerosis apparently necessitates the assumption that altered fat metabolism is the morbid factor in the development of vascular disease in association with diabetes mellitus.

ABSTRACT OF DISCUSSION

DR. J. W. SHERRILL, La Jolla, Calif.: There is no question that diabetic patients who have had the disease for ten years will show arteriosclerosis. Checking over a series of 250 such cases, we came to the conclusion that arteriosclerosis was present in at least 95 per cent. The question of the five year diabetic patient under 40 is a different problem. The method which Dr. Shepardson used, namely, the roentgen ray, does not give the proper percentage of those who have sclerosis, because only the calcified plaques show. Thus not as many cases are discovered as would be found at autopsy. Aschoff quotes Monckeberg as saying that 35 per cent of normal persons under the age of 20 show arteriomyomatosis or arteriomyomatous changes in the aorta. As to whether arteriosclerosis occurs in diabetic patients before treatment with insulin was discovered, I should say that the condition was held in check by diet. Diabetic patients on a low caloric diet do not show progressive arterial changes. Their arteries remain pliable and soft, which, of course, is in keeping with the muscular atrophy from disuse. Likewise, the arterial system is relieved from strain and the arteriosclerosis is nonprogressive. Dr. Shepardson brought up the question of whether diets high in acid produced arterial change. I have had ten dogs on an extremely high acid diet over a period of three years. In making sections from the splenic arteries, they did not show any changes, and the blood pressure remained normal. I have come to the conclusion that acid in the diet is not a factor in arteriosclerosis. Arteriosclerosis is not always present in patients under 40 who have had diabetes for five years. I think that the important factor in treatment is not the diet but the liberal amount

of insulin that is necessary for the proper combustion of the various food substances.

DR. RUSSELL L. CECIL, New York: Dr. Shepardson's interesting problem should be followed up with a study on postmortem material, to determine the incidence of arteriosclerosis in young people (and, I think, in even a younger group, say, of children between the ages of 5 and 15) and to compare that with the incidence of arteriosclerosis in an equal number of children who do not have diabetes. It is an interesting problem, one that I attacked about twenty years ago, before the work on insulin had been carried out by Banting. We studied the pancreas in ninety cases of diabetes. Almost all of the middle-aged patients showed definite arteriosclerosis, and we had the feeling at that time that diabetes in the middle aged was due to arteriosclerosis of the pancreas, or rather to arteriosclerosis of the capillaries in the islands of Langerhans. In diabetes we find hyaline degeneration and sclerosis of the islands similar to the hyaline changes and sclerosis of the glomeruli in chronic nephritis. We felt that it was safe to say that diabetes in middle-aged patients was due to arteriosclerosis of the islands of Langerhans. The only trouble with that theory was that when we examined the pancreas of diabetic children, we rarely found these changes. Then we had to seek for a different theory for the etiology of diabetes in children. We thought that perhaps the disease might be due to a scarcity of the island tissue in children. There seemed to be, on examination of the pancreases of diabetic young people, less island tissue than in those who did not have diabetes. Dr. Shepardson could throw more light on this subject by studying postmortem specimens of children with and without diabetes.

DR. H. CLARE SHEPARDSON, San Francisco: It has been suggested that a study such as this made entirely on children would yield valuable information. Of course, the ideal person in whom to study the effects of the disease is the child, but such a study is hardly feasible for the reason that there are relatively few children who have had diabetes long enough really to develop the effects that apparently result from long exposure.

Part of the discussion of the literature covering this subject was purposely omitted. However, a few series of postmortem examinations on diabetic patients have been recorded. Autopsies on fifty-two of Joslin's patients revealed the presence of arteriosclerosis in all of the patients, nineteen of whom had had the disease for more than five years. Wilder also published a series of eighty-one autopsies on diabetic patients, and noted a high incidence of arteriosclerosis. Gibb and Logan found evidence of vascular disease in sixty-three of 147 necropsies on diabetic patients. The duration of the disease was over five years in only about 15 per cent of these patients. The roentgen ray is obviously inadequate proof that one who does not have roentgenologic evidence of arteriosclerosis has escaped having atheromatous changes in the vascular system. However, when arteriosclerosis is revealed by the roentgen ray it is positive proof that rather advanced vascular changes exist, since only calcification is shown roentgenologically. Newburgh has recently suggested that overfeeding rather than the relative proportions of carbohydrate, protein and fat contained in the food is the cause of high blood fats. This theory is open to question, but the fact remains that these fifty patients have been, as Dr. Sherrill suggested, on slightly undernourishing diets. Consequently, that factor has been eliminated. The whole problem is extremely interesting and is one that has been before the attention of those interested in diabetes for a long time. It is only by analyzing a large series of necropsies on relatively young diabetic patients that we will eventually be able to decide why diabetic patients have arteriosclerosis more commonly than normal persons.

INSULIN INACTIVATION BY HUMAN BLOOD CELLS AND PLASMA IN VITRO

II. EFFECT OF INFECTION ON INSULIN*

SAMUEL KARELITZ, M.D.

SIDNEY D. LEADER, M.D.

AND

PHILIP COHEN, M.D.

NEW YORK

THE EFFECT OF INFECTION ON INSULIN ACTIVITY

The inhibitory action of blood cells and plasma in vitro on insulin activity in the rabbit¹ offered a new means of study of the long known fact that infection has a severe and detrimental effect on the ability of the body to metabolize foods properly, especially foods containing the carbohydrates. This has been demonstrated both for the diabetic and for the nondiabetic person.² Insulin given to a person with an infection has less effect in lowering the blood sugar than it does on a normal person. During such periods, the sugar tolerance is diminished and, according to Richardson and Levine,³ carbohydrate oxidation is diminished.

Explanation for this failure of insulin to have its usual effect during infection has been varied. The general clinical impression that, due to actual pancreatic injury, an inadequate supply of insulin is produced, is not very likely since exogenous insulin is not always effective, and recovery may be so sudden that one could conceive of only a functional change in the pancreas and not an anatomic one. Direct action of toxins on insulin has been suggested, but evidence for this action is lacking. The same holds true for the action of acetone or cholesterol on insulin. Fever, in all likelihood, is not injurious to insulin, since insulin is thermostable. Change in the acid base equilibrium has also been suggested as causative of insulin inactivity. Direct action due to acids or alkali is doubtful, since insulin resists destruction at the p_H ranges compatible with life. However, other functions may be altered by a change in acid-base equilibrium: Mobilization of liver glycogen may be altered.⁴

* Submitted for publication, Oct. 20, 1929.

* From the Departments of Pediatrics and Laboratories, Mount Sinai Hospital.

1. Karelitz, S.; Cohen, P., and Leader, S. D.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro: Effect of Normal and Diabetic Blood on Insulin Action, *Arch. Int. Med.* **45**:546 (April) 1930.

2. Falta, W.: *Klin. Wchnschr.* **3**:1315, 1924.

3. Richardson, H. B., and Levine, S. Z.: *J. Biol. Chem.* **66**:161, 1925.

4. Best, C. H.: *Proc. Inter-State Post-Grad. M. Assembly of North America* of 1927.

as may the liberation of insulin itself and other internal secretions, which might indirectly bring about insulin inhibition or neutralization.

The idea that during infection a state of altered metabolism exists which does not permit proper insulin action, though complex, probably comprises many explanatory factors. The work of Evans and Zeckwer⁵ and Lawrence and Buckley⁶ has been prominent in that direction. They have suggested a stimulation of the thyroid and suprarenal glands to greater activity which leads to increased glycogenolysis and neutralization of insulin action. By injecting *Bacillus coli* or *Bacillus proteus* vaccine into rabbits, Evans and Zeckwer found that a hyperglycemia was produced. They showed that this did not occur if the same experiment was tried after one adrenal was resected and the other denervated. Lawrence and Buckley injected diphtheria toxin into rabbits and found that insulin was then ineffective. They found pathologic changes in the adrenals and thyroid, which they thought was evidence of the stimulation of these glands.

That the thyroid, suprarenal and the pituitary glands are involved in carbohydrate metabolism needs no further confirmation. Adequate clinical and experimental work has been done to prove this, and it is suggestive that other internal secretions also play a part. For example, only one third of the usual dose of insulin is necessary to produce a given insulin effect if parathyroid extract is injected simultaneously.⁷ If parathyroid is given to a rabbit in insulin shock, death follows. We believe that just as the suprarenal and thyroid glands are involved, so may the pituitary, parathyroid, and perhaps other ductless glands be concerned, and be pertinent to the explanation of the problem at hand.

After we had shown that human blood inhibits insulin action in vitro, several problems in the study of insulin action in spontaneous or artificially produced infection-like states presented themselves:

1. Does blood from a person with spontaneous infection have a greater inhibitory action on insulin than normal human blood? The same question might be studied by producing serum sickness, since the mechanism of this disease resembles an infectious diseases. Do leukemic or pus cells have an increased inhibitory effect on insulin action? Do rabbits have increased insulin resistance after injection of vaccines? What are some of the properties of this insulin inhibitory agent and what might it be?

5. Evans, C. L., and Zeckwer, I. T.: Brit. J. Exper. Path. 8:280, 1927.

6. Lawrence, R. D., and Buckley, O. B.: Brit. J. Exper. Path. 8:58, 1927.

7. Cammidge, P. J., and Howard, H. A. H.: J. Metab. Research 6:189 (July) 1924.

EFFECT OF BLOOD FROM PATIENTS WITH PURULENT INFECTION
ON INSULIN ACTION

Applying the same technic in the present studies, as in the experiments described in our first paper, we found that blood from patients with infection affected insulin in a similar manner and degree as did dia-

TABLE 1.—*Rabbit Blood Sugar Curves After Subcutaneous Injection of Laked Blood Cells from Patients with Infection, and Incubated with Insulin at 37 C. for One Hour*

Laked Cells, Amount		Blood Sugar in Mg. per 100 Cc., Hours After Injection			
		0	1	2	3
2 cc.	Case of empyema.....	90	96	94	96
1 cc.	Case of empyema.....	94	92	94	92
		95	84	90	94
1 cc.	Lung abscess.....	96	95	90	95
		88	94	95	95
½ cc.	Case of empyema.....	95	60	70	85
		100	65	68	88
		89	65	71	75
½ cc.	Lung abscess.....	94	90	90	92
		93	76	78	82
		90	84	85	90
		96	73	77	80

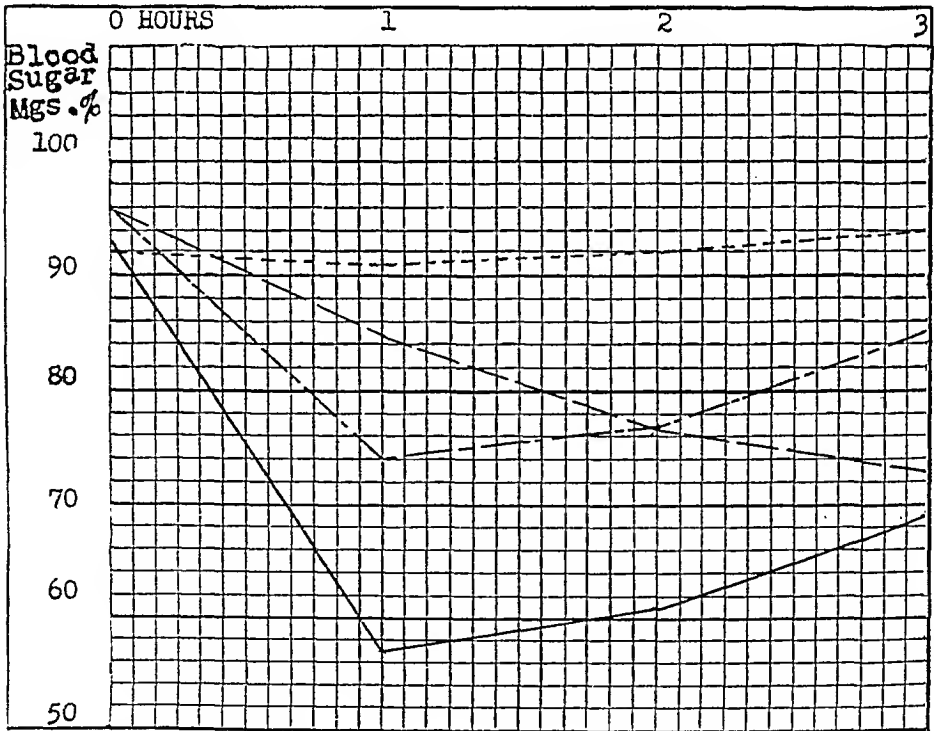


Chart 1.—Effect of laked blood cells from patients with purulent infection. The dotted line indicates results with 1 cc. of cells from a person with infection; dash line, 1 cc. cells from a normal person; dash and dotted line indicates 0.5 cc. cells from a person with infection unbroken line, 0.5 cc. cells from a normal person.

betic blood. The tables and graphs show clearly that in comparison to normal blood about one half as much blood from a patient with infection was needed for the inactivation of three units of insulin.

EFFECT OF BLOOD FROM A PATIENT WITH SERUM SICKNESS ON INSULIN ACTION

Blood taken from a 10 year old child on the first day of an attack of serum sickness which occurred on the tenth day after the injection of diphtheria antitoxin showed marked insulin inactivation. Ten days after the serum sickness had completely disappeared, the blood of this same child showed only the usual amount of insulin inactivation, which was, of course, very much less than that found during the period of her illness.

We believed after sensitizing rabbits to human or horse blood that we could demonstrate an increased resistance to insulin action. The experiments were too few to enable us to draw any definite conclusions. The experiments of Zeckwer and Goodell,⁸ in which they showed tremendous rise in blood sugar of rabbits during anaphylactic shock, though not similar to our work, are suggestive because of the intimate relationship of the conditions of serum sickness and anaphylaxis.

EFFECT OF LEUKEMIC AND PUS CELLS ON INSULIN ACTION

Since leukocytosis accompanies purulent infections and blood cells from patients with infection have increased inhibitory action, we felt that we should know whether white blood cells inactivate insulin more than does a mixture of white and red blood cells. We were not successful in obtaining an adequate amount of white cells from normal blood, and therefore tested the blood cells from a patient with myeloid leukemia whose red cell count was 900,000 and whose white cell count was the same. The leukemic cells showed a greater inactivating power than did normal human blood cells. Pus cells from a patient with pneumococcus empyema were then tested and also showed a stronger inactivating power than normal blood cells.

Shortly after these experiments had been done, Rosenthal and Behrendt⁹ published results similar to ours. They had a specimen of pneumococcus pus, 1 cc. of which was capable of inactivating 500 units of insulin. We therefore tried 10, 20, 30 and 40 units of insulin to 1 cc. of pus, but all our animals developed severe hypoglycemia.

8. Zeckwer, I. T., and Goodell, H.: Blood Sugar Studies; Blood Sugar Changes in Fatal Bacterial Anaphylaxis in Rabbit, *J. Exper. Med.* **42**:57, 1925.

9. Rosenthal, F., and Behrendt, H.: *Ztschr. f. d. ges. exper. Med.* **53**:562, 1926.

ACTION OF INSULIN IN RABBITS AFTER INJECTION OF VACCINE

At the suggestion of one of us (P. C.), we attempted to study the effect of infection, using the method previously used by others¹⁰ for the production of fever in rabbits, by injecting typhoid vaccine.

TABLE 2.—*Effect of Blood from a Patient with Serum Sickness on Insulin Action*

		Blood Sugar in Mg. per 100 Cc., Hours After Injection			
4 cc.	Serum.....	93	92	60	51
2 cc.	Serum.....	84	64	61	50
		92	62	54	50
1 cc.	Laked cells.....	96	88	95	95
		94	95	95	95
½ cc.	Laked cells.....	94	85	75	80
		102	92	82	86

		Blood Sugar in Mg. per 100 Cc., Hours After Injection			
1 cc.	Laked cells.....	88	75	70	76
		93	76	72	75
½ cc.	Laked cells.....	95	50	72	78
		92	55	64	65
		97	60	65	70

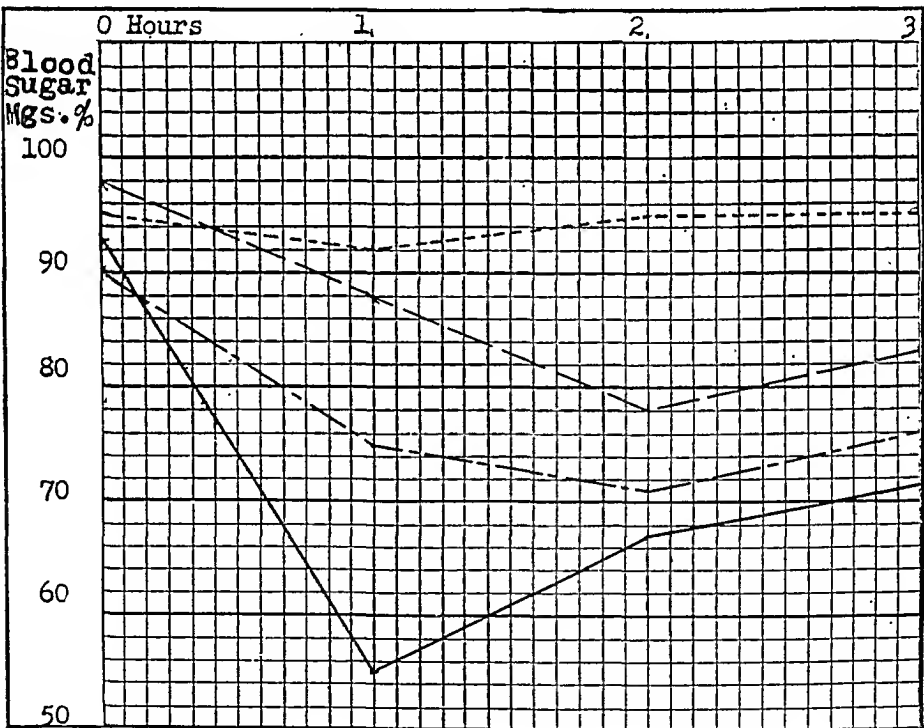


Chart 2.—Serum sickness. Dotted line indicates 1 cc. laked cells in a patient having serum sickness; dash line 0.5 cc. laked cells in a patient having serum sickness; dash and dotted lines, 1 cc. laked cells observed ten days after beginning of serum sickness; unbroken line, 0.5 cc. laked cells observed ten days after beginning of serum sickness.

10. Mcleod, L. L. R.: Personal communication to S. Karelitz. Taite: Tr. Roy. Soc. Canada, 1926.

TABLE 3.—Effect of Leukemic Cells on Insulin Action

		Blood Sugar in Mg. per 100 Cc., Hours After Injection			
(a) 1 cc. Lymphatic leukemia.....	50,000 WBC per mm. ³	96	83	45	35 convulsion
	30 minutes incubation.....	120	70	68	60
		114	65	60	58
		130	88	55	55
(b) 1 cc. Myeloid leukemia	900,000 WBC per mm. ³	126	40	convulsion	
	1 hour incubation	108	60	56	65
		96	58	60	68
		99	45	convulsion	
(c) 2 cc. Same as (b).....	1 hour incubation.....	85	68	88	108
		90	78	100	100
		90	98	100	90
		80	94	100	106

		Effect of Pus on Insulin Action			
1 cc. incubated 15 minutes.....		92	78	72	86
		102	72	70	75
		96	70	70	80
1 cc. with 5 units insulin not incubated		94	55	46	45
		100	58	60	56
		106	60	52	58
		110	58	50	60
2 cc. incubated 15 minutes.....		95	92	85	90
		88	85	85	85
2 cc. incubated 45 minutes.....		90	80	78	80
		92	90	90	90
Average 2 cc. normal cells.....		98	62	51	47
Average 5 cc. normal cells.....		93	78	81	82

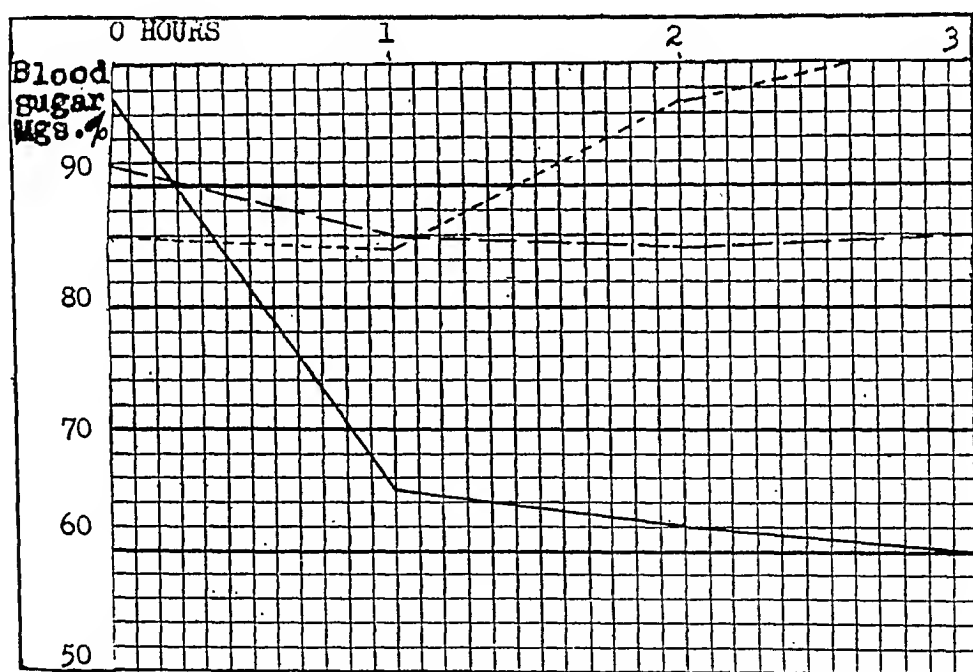


Chart 3.—Effect of leukemic cells and pus as compared to normal blood cells. The unbroken line indicates the effect in patient of 2 cc. normal cells; the dotted line, the effect of 2 cc. leukemic cells on patient; the dash line, 2 cc. pus cells on patient.

When insulin was injected three hours after the starved rabbits had received 500,000,000 dead typhoid bacilli subcutaneously, there was evidence of increased insulin resistance, which lasted from two to five days. This was not a regular response, as can be seen from the accompanying chart. The results obtained using typhoid vaccine closely simulated those found after the use of a staphylococcus vaccine. The action of paratyphoid B vaccine was quite inconsistent, producing a hyperglycemia in some rabbits and no change in others. Our experiments with paratyphoid B were not continued.

The fever which resulted from the injection of vaccine was thought to be the factor that accounted for the poor insulin action. This is doubtful, since insulin is thermostable. With fever there are accompanying body reactions that must be considered. The delayed effect, that is the resistance to insulin after the fever has subsided, is also against the conception that insulin is directly impaired by fever.

Since we began our studies, various publications pertinent to our work have appeared. Minkowski¹¹ suggested that diabetic patients do poorly during infection, possibly because of increased proteolytic enzyme in the blood. Several¹² investigators attempted to prove this point by work similar to ours, such as demonstrating that blood serum or pus from a patient with a purulent infection inhibits insulin. Rosenthal and Behrendt have also shown that liver, spleen or kidney taken from a person dead only six hours inhibited insulin. This power of inactivation was not manifest if the tissues were first boiled. Attempts by the same authors to prevent insulin inactivation, by adding blood serum because of its antitryptic action, failed. Our results with serum alone perhaps explain this failure.

Rosenthal and Behrendt, in an attempt to further their claim that proteolytic enzyme is responsible for the insulin inactivation, mixed rabbit pus with insulin, because of its low enzyme content. They found that it took twenty-four hours for 1 cc. of rabbit pus to inactivate as much insulin as is ordinarily inhibited by 1 cc. of human pus in a few minutes.

Mauriac and Aubertin¹² recently published experiments almost similar to ours showing that normal blood, plasma or cells or both inhibit insulin action. They also found that diabetic blood inhibits insulin action more than does normal blood. They believe an adhesion phenomenon of insulin to blood cells responsible for this inactivation of insulin.

We have considered the enzyme-like action as the most likely explanation for the phenomena that we report. Since we are not able actually to demonstrate the enzyme with accuracy, we preferred to study few of the properties of this insulin-inactivating agent.

11. Minkowski, O.: Insulin in Treatment of Diabetes, *Med. Klin.* **22**:437 (March) 1926.

12. Mauriac, P., and Aubertin, E.: *Compt. rend. Soc. de biol.* **98**:233, 235 and 237 (Jan.) 1928.

TABLE 4.—*Effect of Insulin Three Hours After Injection of Vaccine Into Rabbits*

	Blood Sugar in Mg. per 100 Cc., Hours After Injection			
	0	1	2	3
500,000,000 typhoid bacilli.....	98	70	74	70
	105	72	75	75
	106	88	75	82
	116	90	87	89
	100	55	55	62
	114	77	54	48
	97	86	44	50
	90	97	44	40
	100	66	60	convulsion
	112	76	66	65
	105	90	61	50 convulsion in 4 hours
	115	95	75	70
	100	88	84	76
	90	90	82	72
	132	87	88	90
Effect of Insulin Forty-eight Hours After Injection of Vaccine				
500,000,000 typhoid bacilli.....	110	63	70	72
	115	93	85	77
Effect of Insulin Seventy-two Hours After Injection of Vaccine				
500,000,000 typhoid bacilli.....	115	70	55	60
	120	85	56	70
Effect of Insulin Ninety-six Hours After Injection of Vaccine				
500,000,000 typhoid bacilli.....	97	50	40	40
	105	65	70	65
	120	85	65	45 shock next day
	85	58	50	55
Effect of Insulin Three Hours After Injection of Vaccine into Rabbits				
500,000,000 staphylococcus vaccine.....	98	72	65	74
	108	68	58	50
	100	82	70	72
	104	68	70	45
Effect of Insulin Three Days After Injection of Vaccine				
500,000,000 staphylococcus vaccine.....	112	95	94	85
	105	82	74	75
	105	62	50	convulsion
	110	78	62	convulsion
Effect of Insulin Seven Days After Injection of Vaccine				
500,000,000 staphylococcus vaccine.....	98	68	72	65
	80	55	72	62

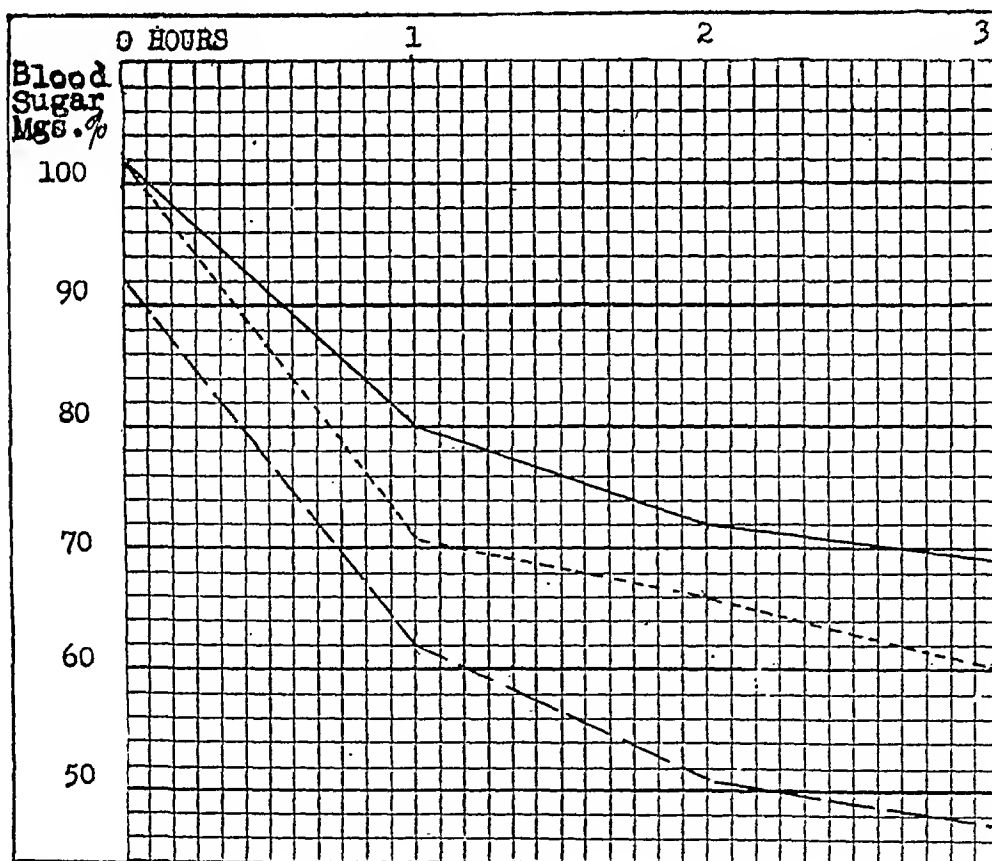


Chart 4.—Effect of vaccine on insulin action. The unbroken line indicates the effect on the vaccine three hours after the administration of typhoid vaccine; the dotted line, the effect three hours after the administration of staphylococcus vaccine; the dash line, the controls of saline solution.

THERMAL EFFECT ON THE INSULIN-INACTIVATING AGENT
IN BLOOD OR PUS

Proteolytic enzymes are usually affected by heat of 55 C. or over. We heated blood plasma, blood cells or pus in a water bath which remained between 57 and 60 C. for one and one-half hours. If insulin were added to the heated blood or pus incubated for one hour at 37 C. in the usual fashion and injected into rabbits, hypoglycemia resulted, thus showing that the inactivating substance is thermolabile. When blood cells were used, the results were inconsistent, unless the cells were laked, which is further evidence that the substance is mainly intracellular.

Scott ¹³ observed that when insulin and pure trypsin were incubated on ice, no insulin destruction or inactivation occurred. We observed the same to be true when blood plasma and insulin were mixed and incubated in an icebox.

IMPORTANCE OF THE DURATION OF INCUBATION

If this agent which inhibits insulin action is enzyme-like, its action should require time. We studied the significance of incubation and found that laked blood cells that had been incubated for ten minutes showed slight action on insulin; with cells that had been incubated for twenty minutes or longer, complete inhibition could be observed.

To rule out the possible effect of the mingling of the blood and insulin under the rabbit's skin for a considerable period of time, the blood and insulin were mixed after the needle had been inserted into the rabbit's heart, and the blood-insulin mixture injected directly into the blood stream. The blood sugar dropped markedly and rapidly, but there was a rapid recovery, so that in the third hour after injection, the blood sugar was normal. This experiment shows that blood requires time to inactivate insulin *in vitro*. The quick recovery is probably due to the rapid excretion of insulin when injected intravenously.

SUMMARY

Summarizing the results of our various experiments, we learn that human blood plasma and, to a greater degree, human blood cells inhibit insulin action *in vitro*. Blood from diabetic patients as well as from patients with purulent infections or artificially produced infection-like conditions, such as serum sickness, causes greater insulin activation in a given time than does normal blood. Blood cells from a patient with myeloid leukemia and pus also show greater insulin inactivating power than do normal blood cells.

13. Scott, D. A.: *J. Biol. Chem.* **63**:641 (April) 1925.

TABLE 5.—Effect of Heating Blood or Pus to 57 C. for from One and One-Half to Two Hours on Its Ability to Inactivate Insulin

Not Heated	Mg. per 100 Ce. of Blood Sugar Hours After Injection			
	0	1	2	3
10 cc. serum.....	95	82	85	80
	95	85	85	88
	92	80	85	87
	82	40	55	80
5 cc. unlaked cells.....	87	52	70	82
	103	82	92	90
	92	80	88	90
	90	77	80	80
5 cc. laked cells.....	90	64	67	70
	103	92	98	98
	96	91	91	95
	114	110	88	100
2 cc. pus.....	90	100	92	90
	90	80	78	80
	92	90	90	90
	95	92	85	90
	88	85	85	85
Heated 10 cc. serum....	110	78	<40	convulsion
	92	62	30	convulsion
	91	68	60	65
	91	74	76	93
5 cc. unlaked cells.....	86	55	65	74
	110	66	68	55
	96	68	58	62
	90	55	68	67
5 cc. laked cells.....	106	45	55	57
	98	80	70	65
	95	78	65	70
	102	60	58	60
2 cc. pus.....	92	62	53	55
	84	46	<40	<40
	93	<30	<30	
Heated ½ Hour				
2 cc. pus.....	92	72	62	60
	90	78	62	70
Effect of Incubation at Icebox Temperature on Ability of Blood to Inactivate Insulin				
10 cc. plasma.....	98	67	60	65
	99	70	65	60
	92	62	58	55
5 cc. cells.....	96	46	40	convulsed
	99	52	40	convulsed
	96	46	convulsed	
10 cc. saline.....	92	72	61	60
	90	62	60	55
<i>ph</i> 9.2.....				

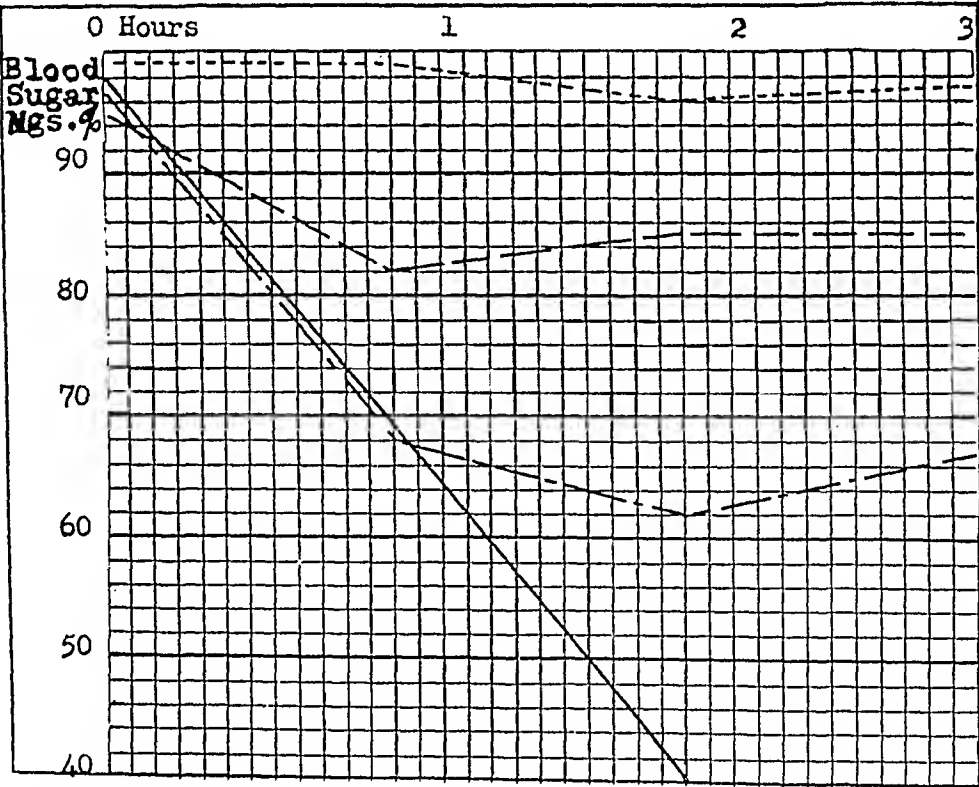


Chart 5.—Effect of heating at 57 C. two hours. The dash line indicates the result after the heating of 1 cc. serum; the unbroken line the result from the heating of 10 cc. serum; the dotted line, after 5 cc. laked calls were heated, and the dash and dot line, the result after the heating of 5 cc. laked cells.

This inactivation seems to act better at mildly alkaline p_H and is ineffective at p_H 6. After being heated from 55 to 60 C. from one to two hours or after incubation at icebox temperature, it also becomes

TABLE 6.—Importance of Incubation in Action of Blood on Insulin in Vitro

		Blood Sugar in Mgs., per Cent Hours After Injection				
		0	1	2	3	
2 cc. laked cells at 60 minutes.....		95	92	90	92	
2 cc. laked cells at 30 minutes.....		93	80	75	90	
		94	92	94	94	
		92	92	92	90	
2 cc. laked cells at 20 minutes.....		85	89	70	80	
		92	85	92	88	
		99	98	92	95	
2 cc. laked cells at 10 minutes.....		93	80	85	86	
		95	80	75	82	
2 cc. laked cells at 0 minutes.....		92	55	63	94	
		95	84	72	92	
		94	82	72	85	
No Incubation—Intravenous		0	½ hour	1 hour	2 hours	3 hours
1 cc. laked cells.....		94	<30	convul.	died	
		97	50	40	50	60

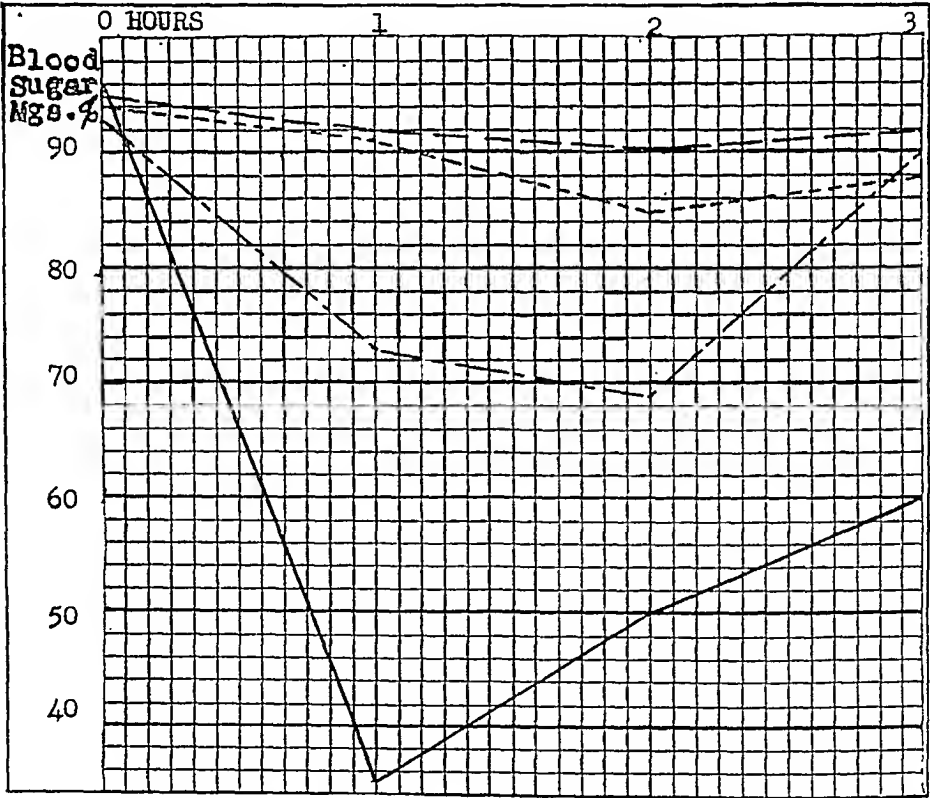


Chart 6.—Effect of incubation of laked cells. The dash line indicates the effect after one hour heating at 37 C.—2 cc.; the dotted line after one-third hour at 37 C.—2 cc., and the unbroken line the effect of 1 cc. heated intravenously.

ineffective. The inactivation requires time and is not present when the blood-insulin mixture is injected directly into the blood stream.

The occurrence of this inactivating substance and its properties as described are so similar to the occurrence and action of enzyme that

we believe that an enzyme, possibly trypsin, or an enzyme-like substance is responsible for the insulin inactivation.

Our observations being limited to the effect of blood outside of the human body on insulin action, we cannot be certain that this phenomenon occurs within the living organism. It is, however, conceivable that when cells are injured as they are during infection, an abnormal state comparable to *in vitro* conditions exists, enabling this substance to act on insulin.

Perhaps in these states of abnormal metabolism, as during infection, inadequate insulin production, neutralization of insulin by action of thyroid, suprarenal, pituitary, and other ductless gland secretions, as well as altered enzyme action throughout the body or in certain locations, are all responsible, acting simultaneously and in varying degrees.

THE TREATMENT OF PERNICIOUS ANEMIA WITH AN AQUEOUS EXTRACT OF LIVER*

H. MILTON CONNER, M.D.

ROCHESTER, MINN.

The use of liver and extract of liver has served to keep alive and relatively well most patients who have thus been treated regularly. In 1926, Minot and Murphy,¹ in an epochal report, showed the value of feeding mammalian liver to patients with pernicious anemia. Whipple, Robscheit-Robbins and Hooper,² in 1920, and Robscheit-Robbins and Whipple,³ in 1925, showed its value in anemia produced by repeated bleeding of animals. In 1927, Minot⁴ reported on the treatment of patients with an effective fraction of liver produced by Cohn. This substance brought about characteristic improvement in the condition of the blood and in the general symptoms. Minot, Cohn, Murphy and Lawson,⁵ in the following year, reported further on the results of treatment with extract of liver.

Porter, Williams, Forbes and Irving,⁶ in 1929, reported on the production of a stable, aqueous extract of liver. Sixteen of the forty-five cases reported by them were under my observation in the hospital at the Mayo Clinic. Four other cases have since been added to the list.

This type of extract has been well tolerated, and few objections to its taste have been heard. The patients have received a regular

* Submitted for publication, Nov. 15, 1929.

* From the Division of Medicine, the Mayo Clinic.

* Read before the Minnesota Society of Internal Medicine, St. Paul, Nov. 11, 1929.

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2. Whipple, G. H.; Robscheit-Robbins, F. S., and Hooper, C. W.: Blood Regeneration Following Simple Anemia: IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets, *Am. J. Physiol.* **53**:236, 1920.

3. Robscheit-Robbins, F. S., and Whipple, G. H.: Blood Regeneration in Severe Anemia: II. Favorable Influence of Liver, Heart and Skeletal Muscle in Diet, *Am. J. Physiol.* **72**:408, 1925.

4. Minot, G. R.: The Treatment of Pernicious Anemia with Liver or an Effective Fraction of Liver, *Tr. Coll. Phys.* **49**:144, 1927.

5. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effect upon Production of Immature and Mature Red Blood Cells, *Am. J. M. Sc.* **175**:599, 1928.

6. Porter, W. B.; Williams, J. P.; Forbes, J. C., and Irving, Hazelwood: Aqueous Extract of Liver: Development and Use in Treatment of Pernicious Anemia, *J. A. M. A.* **93**:176 (July 20) 1929.

hospital diet, so that no part of the results here reported can be attributed to diet. No untoward symptoms have been noted, except occasional diarrhea. The results have been similar to those obtained with liver and with Minot and Cohn's extract of liver. The reticulated erythrocytes began to increase in number a few days after the treatment was started, and a peak was reached in from the third to the twelfth day; usually the decline was rather rapid from that point. In the patients in whom treatment was instituted when the erythrocytes numbered more than from 2,500,000 to 3,000,000 for each cubic millimeter, the increase in the number of reticulated erythrocytes was not great. The number of erythrocytes increased simultaneously.

The initial dose in thirteen cases was 90 cc. daily, whereas in seven it was 180 cc. Usually the dose was reduced to half the original amount about the end of the first week, whereas in two cases the original amount of 180 and 90 cc., respectively, was continued during the entire period of observation in the hospital. In one case, the original amount of 90 cc. was continued for only four days, and then was cut in half, whereas, in another case, the original 180 cc. was continued for eleven days and then reduced to half. The patients usually were sent home to continue taking the amount that had been given them during the latter part of the treatment in the hospital. Three patients said, in answer to a questionnaire, that they had understood that they were to take a teaspoonful thrice daily, whereas they had been instructed to take a tablespoonful. Thus, the amount taken for each day after leaving the hospital, in these three cases, was only 12 cc. In these patients, at the last report, the number of erythrocytes was 4,300,000; 4,680,000, and 3,720,000, respectively. In another patient, the erythrocytes numbered 5,290,000 at the last report. After this patient had left the hospital, he had taken only 24 cc. of extract daily for four months, then 12 cc. daily for five months. One patient, with 3,540,000 erythrocytes at the last report, had substituted another liver extract. Another from whom a final report on the blood has not been received, had taken in all, only twelve bottles of 240 cc. each in the ten months since leaving the hospital.

There was an average increase of exactly 1,500,000 erythrocytes in the twenty-four days of hospital treatment, or 437,500 for each week. The average number of erythrocytes at the time of commencement of treatment was 1,840,000, and at the time of dismissal it was 3,340,000. This is about the same result as that usually obtained with the liver diet. The proportion of red corpuscles which could be identified as reticulated erythrocytes increased to a maximum of 31.8 per cent in one case. Several counts were made each week in each case. In three cases counts of reticulated erythrocytes were made thrice daily until after the peak was reached. When the highest percentage of reticulated cells obtained

in each case had been determined they were averaged; the result was 12.5 per cent. In all but one case, the reticulated erythrocyte count considerably increased if the treatment was instituted when the erythrocyte count was less than 2,500,000. The percentage of reticulocytes was at its peak in an average of seven days after the beginning of treatment. At the time of the patients' dismissal from the hospital, the percentage of reticulocytes had fallen almost to its average original level. The amount of hemoglobin increased from an average of 36.9 to 63.3 per cent, the leukocytes from an average of 5,060 for each cubic milli-

The Treatment for Pernicious Anemia with an Aqueous Extract of Liver

Age, Years and Sex	Before Treatment					On Dismissal					Highest Percentage of Reticulocytes During Treatment	Days in Hospital	Last Report		
	Hemoglobin, percent	Erythrocytes, Millions	Leukocytes, Thousands	Reticulocytes, per Cent	Platelets, Thousands	Hemoglobin, per Cent	Erythrocytes, Millions	Leukocytes, Thousands	Reticulocytes, per Cent	Platelets, Thousands			Hemoglobin, per Cent	Erythrocytes, Millions	Leukocytes, Thousands
61 ♂	30	1.83	6.4	None	140	52	2.80	4.8	2.8	170	13.9	21	75	4.30	9.0
53 ♂	38	2.06	5.3	None	180	68	3.44	6.1	1.0	180	5.2	23	83	4.32	9.3
59 ♂	10	0.79	4.2	3.3	100	50	2.56	7.6	1.8	64	23.1	18	97*	4.08	4.2
37 ♂	40	2.45	3.8	0.6	160	70	3.56	6.1	1.8	240	5.4	25	62	3.20	6.1
42 ♂	30	1.08	5.0	1.2	132	70	3.10	9.4	0.5	240	31.8	27	100	5.29	10.0
36 ♀	25	1.12	4.4	0.5	384	68	3.40	11.6	1.4	240	20.4	34	105	4.68	9.0
62 ♂	30	1.29	4.0	0.5	100	65	3.05	7.0	0.3	200	6.0	29	102	5.28	8.6
61 ♂	31	1.88	4.4	0.4	52	63	3.75	8.6	0.4	280	20.9	20
42 ♀	29	1.83	3.4	0.1	120	64	4.26	6.7	1.1	156	7.6	47	76	3.74	7.8
60 ♀	50	2.27	3.6	2.0	280	66	3.22	4.5	None	260	3.1	23	78	4.36	...
47 ♀	64	2.95	7.3	2.2	60	70	3.34	8.6	None	160	12.2	13	102*	4.38	5.8
65 ♀	30	1.20	5.3	0.3	60	65	3.60	6.4	3.2	200	21.0	23	80	3.98	5.7
53 ♀	63	3.52	5.8	1.0	160	70	3.72	5.1	0.4	160	1.0	26	76	3.72	4.8
74 ♀	29	1.52	4.7	0.1	240	48	2.66	8.6	2.9	280	5.0	23	73	4.11	7.6
55 ♀	35	1.52	8.3	2.5	200	60	3.27	10.3	None	200	6.7	19	72	3.40	9.6
37 ♂	35	1.63	3.0	0.5	128	70	3.85	4.4	0.5	160	13.6	23
58 ♂	38	1.71	5.3	2.7	160	75	3.74	6.6	0.3	200	15.4	42
54 ♂	67	3.54	9.5	0.5	240	70	3.90	6.8	None	280	0.5	19	84	4.61	6.7
71 ♀	30	1.20	3.6	2.4	140	35	2.30	5.2	14.6	80	14.6	9	65	3.54	7.7
53 ♂	34	1.47	4.0	0.6	80	68	3.35	11.1	1.4	320	22.7	22	70	3.80	8.9
Average															
54	36.9	1.84	5.06	1.07	151	63.3	3.34	7.27	1.72	202	12.5	24	82.3	4.16	7.5

* The percentage of hemoglobin was obtained in these cases by multiplying the number of grams per hundred cubic centimeters by 6.

♂ Indicates male and ♀ female.

meter to 7,270, and the platelets from 151,800 for each cubic millimeter to 202,500, during the twenty-four days in the hospital.

No effort was made to study the effect on the bilirubin of the serum or the icterus index, but in the patients who were jaundiced, the jaundice disappeared. No attempt was made to study the gastric acidity. All patients were given dilute hydrochloric acid; usually the dose was 4 cc. three times daily.

The effect of the extract on the weakness, diarrhea, sore tongue, paresthesia and gastric symptoms has been comparable to that seen after the diet of liver has been employed. No patients who had severe symptoms referable to the spinal cord were treated. Protocols of the twenty cases are seen in the accompanying table.

SUMMARY

An aqueous extract of liver made according to the formula of Porter and his associates has been used successfully in the treatment of twenty patients suffering from pernicious anemia. The effect on reticulated erythrocytes, mature erythrocytes and hemoglobin was essentially the same as that obtained with the liver diet or with Minot and Cohn's extract of liver. The effect on the symptoms was similar to that obtained by the other measures.

THE CARDIAC OUTPUT IN HEART DISEASE

I. COMPLETE HEART BLOCK, AURICULAR FIBRILLATION BEFORE AND AFTER THE RESTORATION TO NORMAL RHYTHM, SUBACUTE RHEUMATIC FEVER AND CHRONIC RHEUMATIC VALVULAR DISEASE *

W. CARTER SMITH, M.D.

ATLANTA, GA.

AND

GEORGE L. WALKER, M.D.

AND

HOWARD L. ALT, M.D.

BOSTON

Heart disease and the mechanism of circulatory failure have been the object of much investigative work during the past twenty years. One means of approach to this problem has been a study of the minute volume of the heart. The cardiac output of normal men, when measured at rest, may vary within wide limits, even in the same individual. Burwell and Robinson¹ studied the output of the heart in a series of normal individuals at rest, employing a method similar to the one used in this study. They found that the amount of blood expelled by the heart varied in different subjects from 3.5 liters a minute and 58 cc. a beat to 6.8 liters a minute and 103 cc. a beat. No method of measuring the output of the heart has been satisfactory in congestive failure, as pulmonary edema interferes with gaseous diffusion so as to render the lungs unreliable as a tonometer. For this reason, observations on the output of the diseased heart must be undertaken either in patients with a lesion which eventually will cause failure or in those who have recovered recently from a break in compensation and no longer have pulmonary congestion. Correlation of data derived in this way may give an insight into what occurs when the heart fails. In this study, several types of heart disease were chosen in an attempt to observe the response of the circulation in each form.

REVIEW OF THE LITERATURE

It was not considered within the scope of this paper to include a detailed review of the work that has been done on cardiac output in

* Submitted for publication, Sept. 28, 1929.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Burwell, C. S., and Robinson, G. C.: The Gaseous Content of the Blood and the Output of the Heart in Normal Resting Adults, *J. Clin. Investigation* 1:87, 1924.

heart disease. Only those observations will be mentioned which have a direct bearing on our studies.

Complete Heart Block.—Liljestrand and Zander² studied the cardiac output in a patient, aged 25, with complete heart block. The output of the heart, measured by the nitrous oxide method, was found to be normal. The stroke volume, however, was increased to 128 cc., since the pulse rate was 36 a minute. Lundsgaard,³ in a study of two cases of complete heart block, also found the output per minute to be normal and the stroke volume increased.

The Restoration of Auricular Fibrillation to Normal Rhythm.—Meakins, Dautrebande and Fetter⁴ found an increase in the cardiac output and the alveolar carbon dioxide tension when normal rhythm was established. Stewart⁵ observed an increase in the oxygen saturation of the venous blood of the arm and a decrease in the coefficient of utilization with restoration to normal rhythm, indicating an increased flow of the blood in the arm. He concluded that there is usually an increase in the cardiac output when auricular fibrillation is converted to regular sino-auricular rhythm. Stewart and his co-workers⁶ have shown a decrease of from 20 to 50 per cent in the cardiac output of dogs with an artificially produced auricular fibrillation. This decrease was always accompanied by a pulse deficit. Blumgart and Weiss⁷ have shown a decrease in the velocity of the blood flow in patients with auricular fibrillation.

Chronic Rheumatic Endocarditis.—Meakins et al.⁴ made observations on the output of the heart in five patients with mitral stenosis, using a method similar to the one employed by us. They found a decreased cardiac output which they attributed largely to a diminished stroke

2. Liljestrand, G., and Zander, E.: Studies of the Work of the Heart During Rest and Muscular Activity in a Case of Uncomplicated Total Heart Block, *Acta med. Scandinav.* **66**:501, 1927.

3. Lundsgaard, C.: Untersuchungen über das minuten volumen des Herzens bei Menschen: III. Messungen an zwei Patienten mit totalem Herzblock, *Deutsches Arch. f. klin. Med.* **120**:481, 1916.

4. Meakins, J.; Dautrebande, L., and Fetter, W. J.: Influence of Circulatory Disturbances on Gaseous Exchange of Blood: Blood Gases and Circulation Rate in Cases of Mitral Stenosis, *Heart* **10**:153, 1923.

5. Stewart, H. J.: Blood Gases in Auricular Fibrillation and After Restoration of Normal Mechanism, *Arch. Int. Med.* **31**:871 (June) 1923.

6. Stewart, H. J.; Crawford, H. J., and Hastings, A. B.: The Effect of Tachycardia on the Blood Flow in Dogs, *J. Clin. Investigation* **3**:435, 1926. Stewart, H. J.; Crawford, H. J., and Gilchrist, A. R.: Studies on the Effect of Cardiac Irregularity on the Circulation, *ibid.* **5**:317, 335, 1928.

7. Blumgart, H. L., and Weis, S.: Clinical Studies on the Velocity of the Blood Flow: IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, *J. Clin. Investigation* **5**:343, 1928.

volume. There was also a decrease in the alveolar and arterial carbon dioxide tension of these patients. Lundsgaard,⁸ in a study of the venous blood of the arm in patients with mitral stenosis and auricular fibrillation, found an increase in oxygen unsaturation which he interpreted as indicating a decreased cardiac output. Blumgart and Weiss⁷ found the velocity of the blood flow to be normal in patients with mitral stenosis and insufficiency and in patients with aortic insufficiency, when the heart was compensated and the rhythm was regular.

Alveolar and Arterial Carbon Dioxide, Carbon Dioxide Percentage of the Expired Air, and Respiratory Minute Volume.—Harrop⁹ studied the blood gases by arterial puncture in patients with heart disease, some of whom were in a state of clinical compensation, while others had congestive failure. He found the arterial carbon dioxide to be normal in the compensated patients, but in those with failure there was a definite decrease in the carbon dioxide of the arterial blood. He also found that a rise to normal occurred when compensation became established. Meakins, Dautrebande and Fetter⁴ found a decreased cardiac output and a lowered carbon dioxide tension of the alveolar air and arterial blood in patients with mitral stenosis. There was no clinical evidence of pulmonary congestion in these patients, and the alveolar and arterial carbon dioxide checked well with each other. These patients had recently recovered from a break in compensation, and had a limited cardiac reserve. In a study of the respiration in heart disease, Peabody¹⁰ and Peters and Barr¹¹ pointed out a decrease in the percentage of carbon dioxide in the expired air and an increase in pulmonary minute ventilation in patients with congestive failure.

METHOD

The output of the heart was measured by the method of Field, Bock, Gildea and Lathrop.¹² The procedure consists briefly in measuring the difference in the carbon dioxide content of the arterial and venous blood by the respiratory method, and the total carbon dioxide excretion a minute by means of the Tissot spirometer. The cardiac output is then derived by dividing the amount of

8. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, *J. Exper. Med.* **27**:179, 1918.

9. Harrop, G. A., Jr.: The Oxygen and Carbon Dioxide Content of Arterial and of Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, *J. Exper. Med.* **30**:241, 1919.

10. Peabody, F. W.: Cardiac Dyspnea, *Am. J. M. Sc.* **155**:100, 1918.

11. Peters, J. P., Jr., and Barr, D. P.: Studies of the Respiratory Mechanism in Cardiac Dyspnea: Low Alveolar Carbon Dioxide of Cardiac Dyspnea: Effective Ventilation in Cardiac Dyspnea, *Am. J. Physiol.* **54**:307, 345, 1920.

12. Field, H., Jr.; Bock, A. V.; Gildea, E. V., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, *J. Clin. Investigation* **1**:65, 1924.

carbon dioxide excreted per minute by the arteriovenous difference in carbon dioxide. In these experiments, five samples each of alveolar and "virtual venous" air were collected and analyzed. The oxygen consumption and carbon dioxide excretion were calculated after the expired air had been collected for nine minute periods in a 125 liter spirometer. The carbon dioxide dissociation curve of Bock¹³ was used in computing the results. It was thought unnecessary to determine individual curves for these patients, as the hemoglobin content was normal in each case, and as it had been shown previously⁴ that the alkali reserve of the arterial blood of patients with compensated heart disease is not reduced. The blood pressure was taken twice, and the pulse and respiration were recorded at frequent intervals, the averages of these being the figures used in the accompanying tables and charts. All observations were performed in the postabsorptive, basal state, after the patients had rested from thirty to forty minutes in the reclining chair in which the studies were made. All subjects were in a well compensated condition and without evidence of any congestion in the lungs.

RESULTS

1. COMPLETE HEART BLOCK.—Observations were made in three cases of complete heart block. The results are shown in table 1.

CASE 1.—M. W., a woman, aged 24, a drug clerk, worked daily without experiencing cardiac symptoms. She was compelled to refrain from unusual exertion, however, because of dyspnea and fatigue. There was a history of diphtheria twenty-one years before. At the time of these observations, the heart was slightly enlarged, the rate was 42, the rhythm regular, and the blood pressure 165 mm. systolic and 65 mm. diastolic. The lungs were clear throughout. The vital capacity was 3,600 cc., or 109 per cent of the normal. Studies in this patient showed the minute volume of the heart to average 5.4 liters. The stroke volume was 126 cc., which is considerably above normal.

CASE 2.—J. A., a man, aged 22, was found to have complete heart block seven weeks after an infection of his foot. These studies were made one year and a half later. At this time, moderate activity caused no discomfort. The heart rate was from 31 to 33 a minute, the rhythm was regular and the blood pressure was 119 mm. systolic and 58 mm. diastolic. No râles were heard in the lungs. The vital capacity was 4,300 cc., or 96 per cent of the normal. The output of the heart per minute was 4.7 liters, but there was a marked increase in the stroke volume to 148 cc. associated with the slow heart rate.

CASE 3.—J. E., a man, aged 64, in addition to complete heart block had generalized arteriosclerosis and hypertension. He was ambulatory and led a sedentary life without discomfort. There had been attacks of dizziness which disappeared with the administration of barium chloride. The heart was moderately enlarged. The rate was from 26 to 29 a minute and the rhythm regular. The blood pressure was 181 mm. systolic and 70 mm. diastolic. There was no evidence of moisture in the lungs and there was no peripheral edema. The vital capacity was 3,200 cc., or 71 per cent of the normal. This low vital capacity might suggest that the patient had a mild degree of congestive heart failure. He gave no history of such a condition, however, and the lungs were clear of râles on repeated exami-

13. Bock, A. V.; Field, H., Jr., and Adair, G. S.: Oxygen and Carbon Dioxide Dissociation Curves of Human Blood, *J. Biol. Chem.* **59**:353, 1924.

TABLE 1.—Observations in Patients with Complete Heart Block (Cases 1, 2 and 3)

Date, 1928-1929	Carbon Dioxide Tension		Alveolar, Mm. Hg.	"Virtual" Venous, Mm. Hg.	Arteriovenous Difference, per Cent by Volume	Carbon Dioxide Excreted, Cc. per Min.	Cardiac Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc.	Blood Pressure		Pulse Pressure	Oxygen Used, Cc. per Minute	Respiratory Quotient	Expired Air		Vital Capacity		Comment
	Alveolar, Mm. Hg.	Arteriovenous Difference, per Cent by Volume								Systolic Mm. Hg.	Diastolic Mm. Hg.				Percentage of Oxygen	Percentage of Carbon Dioxide	Respiratory Rate per Minute	Total Ventilation, Liters per Minute	
M. W., a woman, aged 24; height, 163.5 cm.; weight, 63 Kg.; diagnosis, complete heart block																			
January 19.....	38.2	46.9	3.08	181	4.9	42	117	165	65	100	229	0.79	4.08	3.23	18	5.6	3,650	109	No medication
January 26.....	42.4	49.7	3.12	182	5.8	44	132	150	70	80	237	0.77	3.62	2.78	18	6.5	3,500	104	No medication
May 18.....	39.6	46.8	3.22	179	5.6	43	130	155	75	80	219	0.83	3.63	3.01	19	5.9	3,600	107	No medication
J. A., a man, aged 25; height, 178 cm.; weight, 61.1 Kg.; diagnosis, complete heart block																			
December 18.....	40.0	49.2	3.83	182	4.8	31	155	115	50	63	237	0.76	5.14	3.91	11	4.7	4,300	96	No medication
December 20.....	39.3	48.4	3.78	186	4.9	32	164	118	55	63	236	0.79	4.72	3.75	10	5.0	4,300	96	No medication
December 22.....	38.8	49.2	4.58	208	4.5	33	137	125	70	55	238	0.88	4.31	3.80	11	5.5	4,250	95	30 mg. of barium chloride three times a day
J. E., a man, aged 64; height, 173 cm.; weight, 67 Kg.; diagnosis, complete heart block, arteriosclerosis and hypertension																			
November 6....	32.7	42.5	4.64	201	4.3	29	150	100	60	100	251	0.80	3.52	2.82	14	7.1	3,200	71	30 mg. of barium chloride three times a day
November 7....	34.9	44.6	4.56	226	5.0	29	171	185	70	115	231	0.85	3.33	2.86	15	7.9	3,100	69	30 mg. of barium chloride three times a day
November 11....	34.0	44.4	4.01	217	4.7	28	166	180	70	110	253	0.89	3.28	2.82	15	7.7	3,200	71	No medication
November 16....	31.2	44.9	4.84	211	4.4	26	168	200	80	120	243	0.87	3.25	2.81	15	7.2	3,100	69	No medication

nations. This low value may be explained by the fact that he was 64 years old and had a moderate fixation of the wall of the chest. The cardiac output of this patient averaged 4.6 liters a minute and 164 cc. a beat.

The Output of the Heart per Beat and per Minute: Reference to table 1 will show that the minute output of the heart in each of these subjects was well within normal limits. The stroke volume, however, was considerably above the normal level, as was to be expected with the slow pulse rates. The largest stroke volume was found in the patient with the slowest heart rate. This patient was 64 years old and had the more usual type of heart block occurring in older patients and associated with greater myocardial injury and vascular disease. White and Sprague¹⁴ have observed that the ventricular rate in complete heart block is usually faster in patients under 30 years of age than in older persons. This observation is borne out by the three cases here reported.

The Relation Between Blood Pressure and the Cardiac Output: A consideration of the blood pressure of these subjects indicates that there is no consistent relation between the pulse pressure and the cardiac output, either per minute or per beat. The pulse pressure in the first patient was moderately elevated, averaging 87 mm.; that of the second patient was only slightly elevated, averaging 61 mm., while that of the third patient was greatly elevated, averaging 111 mm. The latter case, however, was complicated by arteriosclerosis. This may be an additional factor in causing the increased blood pressure found in this patient, but would not explain that in the first patient as she had no generalized vascular disease. These figures indicate that the stroke volume can be enormously increased with or without a corresponding increase in pulse pressure. This is evidence of the rôle played by the variations in vascular tone. It can be seen also that in these subjects the pulse pressure is not an index of the cardiac output per minute, since with the wide differences in pulse pressure there was very little difference in their circulatory minute volumes. This illustrates the fact observed previously by Burwell and Smith¹⁵ that there is little relation between blood pressure and cardiac output in different individuals.

Vital Capacity, Alveolar Carbon Dioxide, Carbon Dioxide of the Expired Air and Respiratory Minute Ventilation: The two younger patients had a normal vital capacity, associated with normal alveolar carbon dioxide tension, carbon dioxide percentage of the expired air and respiratory minute ventilation. The older subject, however (case 3), had a lower alveolar carbon dioxide tension and carbon dioxide per-

14. White, P. D., and Sprague, H. B.: High Grade Heart Block Under Thirty Years of Age, *M. Clin. North America* 10:1235, 1927.

15. Burwell, C. S., and Smith, W. C.: The Output of the Heart in Patients with Abnormal Blood Pressures, *J. Clin. Investigation* 7:1, 1929.

TABLE 2.—Observations in Patients with Auricular Fibrillation Before and After Restoration of Normal Rhythm (Cases 4, 5 and 6)

Date, 1928-1929	Carbon Dioxide Tension		Arteriovenous Difference, per Cent by Volume	Carbon Dioxide Excreted, Cc. per Min.	Cardiac Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc.	Blood Pressure		Pulse Pressure	Oxygen Used, Cc. per Minute	Respiratory Quotient	Expired Air		Vital Capacity		Comment		
	Alveolar, Mm. Hg.	"Virtual" Venous, Mm. Hg.						Systolic Mm. Hg.	Diastolic Mm. Hg.				Percentage of Oxygen	Percentage of Carbon Dioxide	Cubic Centimeters	Per Cent of Normal			
P. R., a man, aged 43; height, 176 cm.; weight, 68 Kg.; diagnosis, auricular fibrillation and syphilis																			
December 21.....	32.9	46.2	6.32	185	2.9	100	29	112	80	32	213	0.87	3.66	3.17	14	5.8	4,200	91	Fibrillation; 19 pulse deficit; no digitalis
December 27.....	36.5	48.8	5.47	196	3.6	90	40	108	85	23	215	0.91	3.33	3.04	16	6.5	4,300	94	Fibrillation; 19 pulse deficit; no digitalis
December 28.....	35.2	48.6	6.06	194	3.2	80	40	110	85	25	207	0.94	3.13	2.93	17	6.6	4,250	92	Fibrillation; 19 pulse deficit; no digitalis
December 29.....	39.0	50.4	4.75	173	3.6	76	48	100	75	25	202	0.86	3.55	3.04	16	5.7	4,600	100	Fibrillation; 7 pulse deficit; 1.0 Gm. of digitalis
December 31.....	39.4	50.8	4.80	204	4.3	82	52	112	80	32	214	0.96	3.15	3.01	16	6.8	4,600	100	Fibrillation; no pulse deficit; 1.5 Gm. of digitalis
January 3.....	40.0	49.4	3.92	178	4.6	78	58	112	80	32	213	0.83	3.80	3.15	15	5.3	4,600	100	Fibrillation; no pulse deficit; 1.6 Gm. of digitalis
January 4.....	38.9	49.7	4.74	164	3.5	73	48	118	84	34	206	0.80	4.22	3.36	14	4.9	4,500	98	Regular; quinidine
January 7.....	41.6	51.7	4.22	174	4.1	60	68	110	80	30	211	0.82	3.78	3.11	15	5.6	95	Regular; quinidine
January 8.....	38.3	50.1	5.09	179	3.5	72	49	116	84	32	209	0.89	3.58	3.06	15	5.8	4,400	95	Regular; quinidine
January 16.....	28.5	49.9	5.01	169	4.0	77	52	118	85	33	237	0.84	3.54	2.98	13	6.7	4,400	95	Regular; quinidine

T. H., a man, aged 56; height, 171 cm.; weight, 75.3 Kg.; diagnosis, mitral stenosis and insufficiency, auricular fibrillation.																			
January 27.....	32.8	43.4	4.94	176	3.6	80	45	122	75	47	206	0.86	3.30	2.82	17	5.8	3,100	63	Fibrillation; no pulse deficit; no digitalis
February 1.....	32.4	43.1	4.90	169	3.5	81	43	118	80	38	225	0.77	3.50	2.68	19	6.4	3,100	66	Fibrillation; no pulse deficit; no digitalis
February 4.....	33.4	45.4	5.39	174	3.2	56	58	118	86	32	219	0.79	3.55	2.82	18	6.2	3,000	61	Sino-auricular rhythm, 12 auricular premature contractions
February 5.....	33.2	44.0	4.94	170	3.4	84	41	118	90	28	218	0.78	3.53	2.75	17	6.2	2,950	63	Fibrillation; no pulse deficit; quinidine
February 10.....	35.9	45.2	4.69	174	4.3	58	74	130	86	44	225	0.77	3.80	2.93	18	5.9	3,000	64	Regular rhythm, no premature contractions
April 25.....	37.6	46.6	4.18	189	4.5	60	75	130	90	40	232	0.81	3.62	2.94	17	6.4	Regular rhythm, no premature contractions
F. M., a man, aged 25; height, 178 cm.; weight, 65.1 Kg.; diagnosis, mitral stenosis and insufficiency, auricular fibrillation.																			
November 13....	40.2	51.0	4.89	203	4.3	63	68	120	80	40	244	0.85	3.59	3.03	15	6.8	5,000	110	Fibrillation; no pulse deficit; digitalis
November 14....	39.8	51.3	4.84	62	..	124	85	39	...	0.83	3.56	2.97	16	...	5,000	110	Fibrillation; no pulse deficit; digitalis
November 20....	38.1	49.0	4.53	203	4.5	69	65	115	78	37	253	0.80	3.67	2.95	16	6.9	5,300	115	Fibrillation; no pulse deficit; no digitalis
November 24....	37.5	49.4	5.02	213	4.3	72	59	106	76	30	277	0.77	3.71	2.86	18	7.5	5,300	115	Fibrillation; no pulse deficit; no digitalis
November 26....	37.3	49.6	5.19	212	4.1	60	68	108	70	38	262	0.81	3.57	2.89	18	7.3	5,400	117	Fibrillation; no pulse deficit; digitalis
November 30....	37.0	45.5	3.21	216	6.8	79	86	160	58	42	270	0.80	3.82	3.06	16	7.1	5,300	115	Regular rhythm; quinidine
December 1.....	40.7	48.5	3.43	202	5.9	70	84	115	76	39	254	0.80	4.19	3.33	16	6.1	5,500	118	Regular rhythm; quinidine
December 2.....	39.3	49.1	4.18	221	5.3	72	74	120	78	42	256	0.86	3.89	3.35	14	6.6	5,500	118	Regular rhythm; quinidine
December 4.....	38.9	47.9	3.83	213	5.6	74	75	122	80	42	252	0.84	3.65	3.08	16	6.9	5,600	121	Regular rhythm; quinidine
December 6.....	38.2	47.4	3.96	204	5.2	72	72	122	80	42	296	0.74	4.41	3.26	12	6.3	5,400	116	Regular rhythm; no quinidine
December 7.....	38.7	48.8	4.37	219	5.0	70	72	120	80	40	248	0.88	4.00	3.56	10	6.2	5,400	116	Regular rhythm; no quinidine
December 10.....	39.8	47.9	3.87	203	5.3	71	74	122	82	40	239	0.85	4.02	3.41	12	6.0	5,400	116	Regular rhythm; quinidine
December 11.....	39.3	48.1	3.86	210	5.4	76	71	122	84	38	262	0.80	4.21	3.47	16	6.0	5,400	116	Regular rhythm; quinidine
January 10.....	39.4	48.6	3.82	230	6.0	82	73	128	88	40	285	0.81	4.25	3.42	14	6.7	5,500	118	Regular rhythm; quinidine

centage of the expired air and a greater respiratory minute ventilation. These differences were probably related to the more advanced myocardial and vascular disease in the older subject.

The Effect of Barium Chloride on the Circulation in Complete Heart Block: The observation that barium chloride relieves the attacks of syncope in Stokes-Adams disease, as reported by Cohn and Levine,¹⁶ led us to study the effect of this drug on the circulation in two of our subjects (cases 2 and 3). Thirty milligrams was given three times daily. Reference to table 1 will show that no appreciable changes could be detected in the pulse rate, cardiac output or stroke volume under the influence of this drug. A slight decrease in pulse rate did occur, however, when barium chloride was discontinued in case 3. No corresponding change occurred in the cardiac output.

From our studies of these patients, it seems that complete heart block per se does not alter the efficiency of the circulation in the basal state. This is borne out by the normal cardiac output per minute, vital capacity, alveolar carbon dioxide and respiratory minute ventilation found in the two younger patients (cases 1 and 2), in whom there was no evidence of cardiac disease other than the heart block. This, too, is entirely in accord with the results of simple clinical observation of patients of this type.

Since the observations in the two younger patients (cases 1 and 2) were normal when they were studied in the basal state, it was thought that their response to exercise would be of interest. This is reported in the second paper of this series.

2. THE RESTORATION OF AURICULAR FIBRILLATION TO NORMAL RHYTHM.—In this group, three patients were studied, one of whom had auricular fibrillation without any demonstrable valvular lesion, and the other two mitral stenosis and insufficiency. The response to digitalis therapy was also studied in two of these patients, before normal rhythm was established. The results are shown in table 2 and in chart 1.

CASE 4.—P. R., a man, aged 43, was admitted to the hospital with shortness of breath and a totally irregular pulse ten days before these studies were begun. The heart was not enlarged. The blood pressure was 110 mm. systolic and 80 mm. diastolic. The blood Wassermann reaction was positive. At the time of these studies the ventricular rate was 100 with a pulse deficit of from 15 to 20 a minute. The heart sounds were normal and only a faint systolic murmur could be heard at the apex. There was no evidence of congestive failure at this time and the lungs were entirely clear. The vital capacity was 4,200 cc., or 91 per cent of the normal.

Observations were made on this patient before the use of any medication, again when digitalis was given, and finally after normal rhythm was restored with quinidine sulphate. The output of the heart averaged 3.2 liters a minute when no

16. Cohn, A. E., and Levine, S. A.: Beneficial Effects of Barium Chloride on Adams-Stokes Disease; Report of Three Cases, *Arch. Int. Med.* **36**:1 (July) 1925.

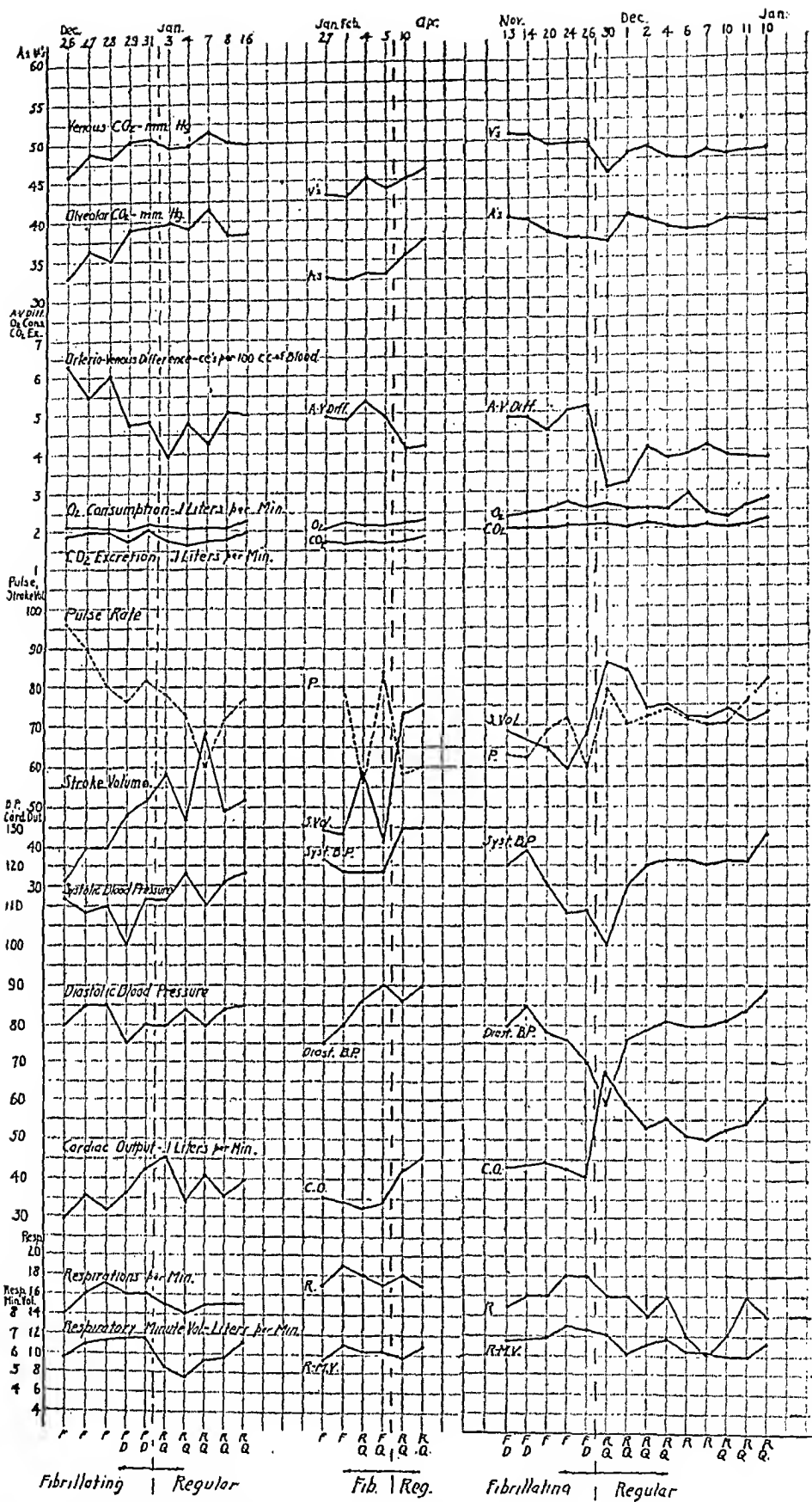


Chart 1.—Graphic representation of the observations on the circulation and respiration of three patients with auricular fibrillation before and after the restoration of normal rhythm; case 4, a man, aged 43, with auricular fibrillation and syphilis; case 5, a man, aged 56, with mitral insufficiency and stenosis, and auricular fibrillation; case 6, a man, aged 25, with mitral insufficiency and stenosis, and auricular fibrillation.

medication was being given. Following the administration of digitalis, the ventricular rate decreased from 100 to 79 and the pulse deficit disappeared. At the same time, the cardiac output rose to an average of 4.2 liters a minute, an increase of 31 per cent, and the stroke volume increased from 37 cc. to 53 cc. Following restoration to normal rhythm, there was no further increase in the cardiac output.

CASE 5.—T. H., a man, aged 56, admitted to the hospital because of attacks of syncope, showed no symptoms of congestive heart failure. The heart was slightly enlarged, the rhythm was totally irregular and the rate 80 a minute, but there was no pulse deficit. There were the usual signs of mitral stenosis and insufficiency. The blood pressure was 120 mm. systolic and 78 mm. diastolic. There was normal resonance over the lungs, and no râles could be heard on repeated examinations. The vital capacity was 3,100 cc., or 66 per cent of the normal. Here, as in case 3, the low vital capacity might lead one to suspect a mild degree of congestive heart failure. The fact that the patient worked daily as a pressman without discomfort, and that the lungs, liver and extremities at no time showed any evidence of congestion, led us to believe that there could be no impairment of gaseous diffusion between the alveolar air and the pulmonary circulation.

Studies in this case were begun before the use of any medication. Digitalis was never given to this patient, as there was no congestive failure and the heart rate was slow and without pulse deficit. The minute output of the heart was 3.5 liters, and the stroke volume was 44 cc. Following these observations, he was given quinidine sulphate and a sino-auricular rhythm was established. The first twenty-four hours after this change, the rhythm was quite irregular, because of the occurrence of about twelve auricular premature contractions a minute. The next day there was a return to auricular fibrillation. The dosage of quinidine was then increased and the heart assumed a slow, regular rhythm, at a rate of 59 beats a minute. No change occurred in the cardiac output when sino-auricular rhythm was first established with the auricular premature contractions, nor was there any change with return to auricular fibrillation. When the regular sino-auricular rhythm was finally established, however, without premature contractions, the cardiac output increased from an average of 3.4 liters to 4.4 liters, an increase of 29 per cent. There was a corresponding increase in the stroke volume from an average of 44 cc. to 74 cc.

CASE 6.—F. M., a man, aged 25, was admitted to the hospital in a state of mild cardiac decompensation, brought about by two months of hard manual labor to which he was unaccustomed. The heart was not enlarged; the rhythm was totally irregular, and the rate was slow and without pulse deficit, even before the use of digitalis. There were the auscultatory signs of mitral insufficiency and stenosis. The blood pressure was 120 mm. systolic and 80 mm. diastolic. One week later, he was symptom-free and without evidence of congestive failure. The ventricular rate was 68 and there was no pulse deficit. The lungs were clear throughout and there was no peripheral edema. The vital capacity was 5,000 cc., or 110 per cent of the normal.

Therapy with digitalis was begun the day of admission to the hospital. One week later, there were no signs of congestive failure and the special studies were begun. The drug was then omitted for ten days and the observations were repeated. Following this, the patient was again given full doses of digitalis and the studies were repeated, and finally after normal rhythm had been restored with quinidine sulphate. The cardiac output was 4.3 liters a minute

when first observed under the effect of the digitalis. The stroke volume was 68 cc. Neither omission of the drug for ten days nor the second period of digitalization caused any appreciable change in the cardiac output. There was a slight increase in the heart rate when digitalis was omitted, but no pulse deficit appeared. Following restoration to normal rhythm, the cardiac output increased to an average of 5.6 liters a minute, a rise of 30 per cent. At the same time, there was an increase in the stroke volume from an average of 65 cc. to 75 cc., and the heart rate increased from an average of 65 to 74 a minute.

The Output of the Heart: A review of the response of these patients to digitalis and quinidine therapy is necessary for comparison. The first patient (case 4) did not have mitral stenosis. The heart rate was rapid and there was a pulse deficit of from 15 to 20 a minute during fibrillation. Digitalis decreased the heart rate and abolished the pulse deficit, and the output of the heart increased 31 per cent. Restoration to normal rhythm caused no further increase in the cardiac output. The second and third patients (cases 5 and 6) had mitral stenosis. Their heart rates during fibrillation were slow and without pulse deficit. Digitalis caused no change in the cardiac output of one of them and was not given to the other. Restoration to normal rhythm, however, caused a 29 per cent increase in the output of the heart in one and a 30 per cent increase in the other.

We had the opportunity of observing in one patient (case 5) the output of the heart when the rhythm was irregular from auricular fibrillation on one day and irregular from auricular premature contractions on the next. These two conditions were quite similar clinically, and an electrocardiogram was necessary to determine the type of arrhythmia. The return of auricular fibrillation on the third day allowed us again to measure the output of the heart under this condition. The cardiac output was found to be the same with the two types of arrhythmia. Thus, the irregularity produced by many auricular premature contractions may have the same effect on the cardiac output as the irregularity of auricular fibrillation.

The Effect of Pulse Deficit on the Output of the Heart in Auricular Fibrillation: This effect is well illustrated in case 4 in which there was a pulse deficit of from 15 to 20 a minute; the elimination of which by digitalis was associated with a substantial increase in the cardiac output. No further increase occurred when regular rhythm was established. This patient had no mechanical obstruction at the mitral orifice.

The Effect of Mitral Stenosis on the Output of the Heart in Auricular Fibrillation: Neither of the two patients with mitral stenosis (cases 5 and 6) had a pulse deficit. There was a definite increase in the cardiac output when sino-auricular rhythm was established without premature contractions. Thus it seems, in these subjects, that with a mechanical obstruction at the mitral orifice, auricular systole is essential in the

maintenance of a normal output of the heart. Without obstruction at the mitral orifice, as in case 4, auricular fibrillation, at the time there was no pulse deficit, had no influence in reducing the cardiac output.

As it has been shown in the patients studied that either pulse deficit or mitral stenosis cause a decrease of from 29 to 31 per cent in the cardiac output when there is auricular fibrillation, it is only reasonable to suppose that when these conditions coexist there will be an even greater reduction in the output of the heart. These data may be of some use in the selection of patients who would be benefited by the restoration of auricular fibrillation to normal rhythm.

Alveolar Carbon Dioxide, Carbon Dioxide Percentage of the Expired Air, Arteriovenous Difference, Respiratory Minute Ventilation and Vital Capacity: In each of the three cases under discussion the increase that occurred in the cardiac output was accompanied by an increase in the alveolar carbon dioxide and in the carbon dioxide percentage of the expired air, a decrease in the arteriovenous difference in carbon dioxide, and some decrease in the respiratory minute ventilation. The decrease in the arteriovenous difference resulted largely from the elevation in the alveolar carbon dioxide, with a lesser rise in the venous level. These changes are illustrated in chart 1. There was no significant change in the vital capacity of any of these subjects with the increase in cardiac output.

3. SUBACUTE RHEUMATIC FEVER.—This section considers the observations made in one case at irregular intervals for a period of seven months. The results are shown in table 3 and in chart 2.

CASE 7.—G. P., a graduate nurse, aged 23, living in the hospital, complained of palpitation, precordial pain and slight breathlessness of two months' duration. Low grade fever and an overactive heart were associated with these symptoms. They continued intermittently for a period of seven months. At the end of this time, an acute, rapidly shifting, multiple arthritis developed. There was no clinical evidence of a definite valvular lesion, nor was the heart enlarged. No râles were ever heard in the lungs. The basal blood pressure was quite unstable, fluctuating between 142 and 118 mm. systolic and 90 and 65 mm. diastolic. The vital capacity was 3,400 cc. or 112 per cent of the normal.

The symptoms were marked and the heart was overactive during the first six weeks that the patient was observed. She was then admitted to the hospital for eleven days because of lack of improvement. This was followed by two months of convalescence during which she was without symptoms. She then returned to work and felt well, except for occasional palpitation and precordial pain, until the onset of the acute arthritis seven months after these studies were begun.

Seven observations were made during the first six weeks. Symptoms were quite marked during this time, but she continued at work. The average output of the heart was 4 liters a minute, the pulse rate was 82 and the stroke volume was 49 cc. There was a gradual decrease in the cardiac output during the time between the first observation and admission to the hospital six weeks later.

Clinical improvement began soon after entrance to the hospital, and by the sixth day the patient was feeling quite well. At this time, the cardiac output had increased 65 per cent to 6.6 liters a minute, and the stroke volume had risen from 49 to 84 cc., an increase of 71 per cent. The pulse rate, however, decreased very little until several days later. The elevated cardiac output was maintained during the two months' period of convalescence and after she resumed her duties as a nurse. With the onset of acute arthritis, there were a few mild cardiac symptoms, but no further changes occurred in the circulatory mechanism except for an increased pulse rate.

The Output of the Heart per Minute and per Beat: When the output of the heart is correlated with the clinical course in this patient, the relation between the higher level of cardiac output and clinical improvement is quite striking. The lower output, observed when the symptoms were quite marked, may be explained by a myocardial fatigue, brought about by the prolonged rheumatic infection plus continued physical activity.

The Relation Between the Blood Pressure and the Cardiac Output: The fluctuations in blood pressure that occurred during the seven months in no way paralleled the changes in cardiac output (chart 2). In spite of the variable systolic and diastolic pressures, the pulse pressure remained remarkably constant throughout, having an average of 58 mm. with a cardiac output of 4 liters a minute, and again of 58 mm. when the output was 6 liters. Here, as in the patients with complete heart block, there was no constant relation between the blood pressure and the output of the heart, per minute or per beat.

Alveolar Carbon Dioxide, Carbon Dioxide Percentage of the Expired Air, Arteriovenous Difference in Carbon Dioxide, Respiratory Minute Ventilation and Vital Capacity: It can be seen from chart 2 that the alveolar carbon dioxide associated with the lower cardiac output was much less than that found when the cardiac output had increased. The arteriovenous difference, then, was decreased by a relatively greater change in the alveolar than in the venous level. It was also found that the percentage of carbon dioxide in the expired air increased with the elevation in cardiac output, and that the respiratory minute ventilation decreased. The vital capacity remained practically unchanged throughout the seven months of observation.

The Relation of the Cardiac Output to the Heart Sounds: During the first six weeks that the patient was observed, the heart sounds were loud and snapping and the rate was somewhat increased. The cardiac output at this time ranged from 3 to 4 liters a minute. Two months later, the heart sounds were of normal intensity, with a slower rate, and the output of the heart was well above 6 liters a minute in repeated experiments. Increased intensity of the heart sounds, therefore, does not necessarily indicate an increase in the cardiac output.

TABLE 3.—Observations Over a Period of Seven Months in a Patient with Subacute Rheumatic Fever (Case 7)

Date, 1928-1929	Carbon Dioxide Tension		Arteriovenous Difference, per Cent by Volume	Carbon Dioxide Excreted, Cc. per Min.	Cardiac Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc.	Blood Pressure		Pulse Pressure	Oxygen Used, Cc. per Minute	Respiratory Quotient	Expired Air		Vital Capacity		Comment		
	Alveolar, Mm. Hg.	"Virtual" Venous, Mm. Hg.						Systolic Mm. Hg.	Diastolic Mm. Hg.				Percentage of Oxygen	Percentage of Carbon Dioxide	Respiratory Rate per Minute	Total Ventilation, Liters per Minute		Cubic Centimeters	Per Cent of Normal
G. P., a woman, aged 22; height, 157 cm.; weight, 53 Kg.; diagnosis, subacute rheumatic fever																			
November 2.....	32.0	39.3	3.47	169	4.9	84	58	112	80	62	212	0.80	3.51	2.79	20	6.0	3,400	112	Working; symptoms marked
November 6.....	33.9	41.8	3.47	174	5.0	80	63	127	70	57	226	0.77	3.88	2.98	16	5.8	3,400	112	Working; symptoms marked
November 13.....	33.7	43.1	4.04	160	3.9	76	52	138	80	58	204	0.78	3.82	2.99	16	5.3	3,400	112	Working; symptoms moderate
November 22.....	30.1	39.7	4.64	147	3.2	77	41	123	72	56	221	0.67	4.61	3.07	15	4.8	3,330	107	Working; symptoms moderate
November 25.....	29.9	39.3	4.54	142	3.1	82	38	125	70	55	209	0.68	3.81	2.61	18	5.4	3,300	108	Working; symptoms moderate
December 3.....	29.6	39.8	4.85	180	3.7	81	45	118	65	53	223	0.82	3.69	2.99	17	6.2	Working; symptoms moderate
December 12.....	29.6	39.3	4.69	198	4.2	89	48	132	65	67	230	0.86	3.15	2.71	19	7.3	3,200	109	Working; symptoms moderate
December 14.....	33.5	41.6	3.51	167	4.8	92	52	135	75	60	237	0.71	4.06	2.87	18	5.8	In hospital; symptoms moderate
December 15.....	40.5	46.3	2.62	171	6.5	87	75	110	70	70	230	0.74	4.23	3.14	14	5.4	In hospital; symptoms few
December 17.....	41.4	48.0	2.81	175	6.2	96	65	135	78	57	225	0.78	4.22	3.28	15	5.3	In hospital; symptoms few
December 19.....	41.8	47.9	2.44	160	6.6	78	81	125	65	60	211	0.75	4.35	3.23	15	4.9	3,350	113	In hospital; symptoms few
December 24.....	37.3	44.3	3.06	156	5.1	81	63	136	85	51	193	0.81	3.91	3.16	15	4.9	3,660	117	Discharged; symptoms very few
January 14.....	40.1	46.4	2.69	168	6.5	78	83	135	78	57	217	0.74	4.61	3.43	14	4.9	3,100	99	Convalescing; symptoms very few
February 11.....	36.8	43.4	2.91	183	6.3	75	84	138	84	54	230	0.80	4.25	3.38	12	5.4	3,150	101	Convalescing; no symptoms
February 24.....	37.5	43.7	2.68	164	6.1	77	80	140	80	60	217	0.76	4.43	3.36	12	4.9	3,400	111	Working; symptoms very few
May 14.....	36.5	43.8	3.20	190	5.9	93	64	142	90	52	236	0.81	3.97	3.20	16	5.8	3,200	103	Acute arthritis; symptoms moderate

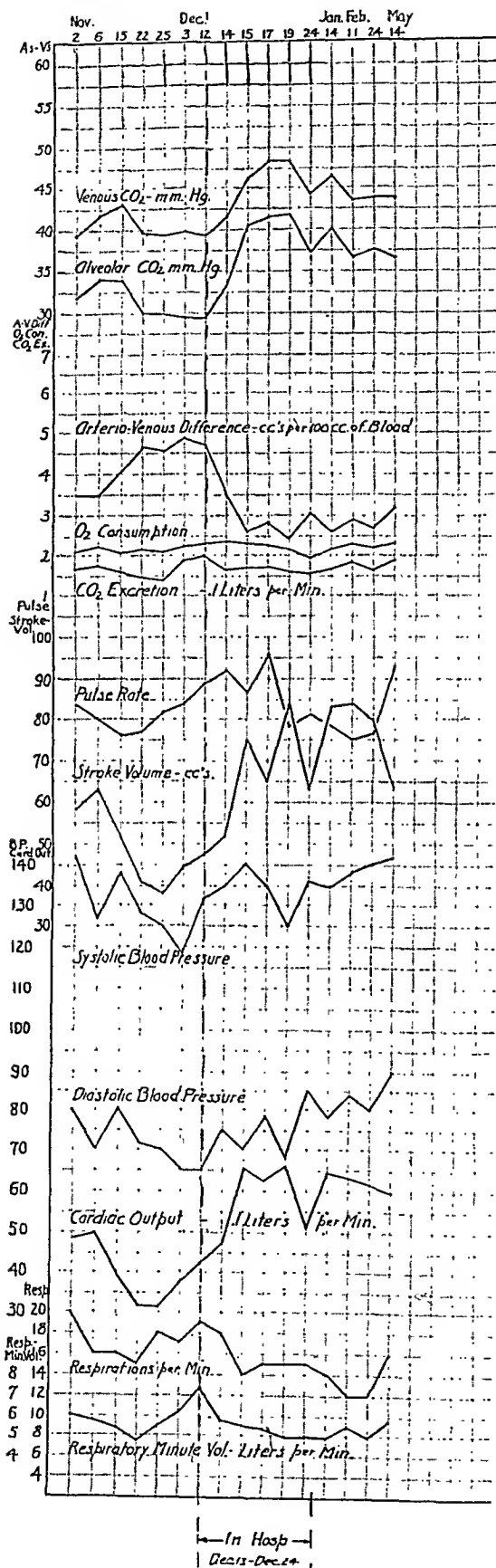


Chart 2.—Graphic representation of the changes that occurred in the circulation and respiration of a patient with subacute rheumatic fever over a period of seven months; case 7, a woman, aged 22, with subacute rheumatic fever.

4. CHRONIC RHEUMATIC VALVULAR DISEASE.—This group includes three patients with well established rheumatic valvular disease, one of whom had aortic stenosis and insufficiency and the other two combined mitral and aortic disease.

CASE 8.—*Aortic Stenosis and Insufficiency*.—J. B., a man, aged 52, was admitted to the hospital because of substernal pain of two years' duration and orthopnea for the past four days. There was an indefinite history of rheumatic fever twenty years before. The heart was considerably enlarged, the rate was 110 a minute and the rhythm regular. There were the auscultatory signs and the thrill of aortic stenosis and insufficiency. The blood pressure was 110 mm. systolic and 55 mm. diastolic.

Eight days after admission to the hospital, these studies were begun. At this time, there were no signs of congestive heart failure; there was no dyspnea, and the lungs were clear throughout. The vital capacity was 3,000 cc., or 70 per cent of the normal. In spite of this lowered vital capacity, we felt that diffusion could take place between the blood and the alveolar air unimpaired, because there were no râles in the lungs at any time.

The output of the heart in this patient was entirely within the range of normal, averaging 4.4 liters a minute and 57 cc. a beat (table 4).

CASE 9.—*Mitral Stenosis and Insufficiency and Aortic Insufficiency (Mild)*.—S. T., a youth, aged 16, had been observed in the outpatient department at irregular intervals for the past three years. He led an active life, playing basketball three times a week without discomfort. The heart was slightly enlarged, the rate and rhythm were normal, and the blood pressure averaged 117 mm. systolic and 65 mm. diastolic. The lungs were entirely clear and without râles, and the vital capacity was 3,000 cc., or 73 per cent of the normal.

The output of the heart in this subject averaged 4.9 liters a minute and 61 cc. a beat (table 4).

CASE 10.—*Aortic Insufficiency, and Mitral Stenosis and Insufficiency (Advanced)*.—I. C., a youth, aged 18, had been admitted to the hospital on three occasions during the past three years. Four hundred cubic centimeters of fluid was removed from the pericardial cavity on the first admission. He was found to have well established valvular disease at this time. There had been recurrent attacks of rheumatic fever since he was 7 years old. The heart was markedly enlarged, and the rhythm was regular at a rate of 67 a minute. The blood pressure was 140 mm. systolic and 20 mm. diastolic. No râles were heard in the lungs and the vital capacity was 3,400 cc., or 77 per cent of the normal.

The cardiac output averaged 4 liters a minute and 59 cc. a beat on two observations.

The Output of the Heart per Minute and per Beat: In spite of the well established valvular lesions, the output of the heart in these three patients fell within normal limits. These observations are in accord with those of Blumgart and Weiss,⁷ who found that the velocity of the blood flow is normal in patients with compensated rheumatic valvular disease.

The Relation Between Blood Pressure and the Cardiac Output: Here, as well as in the patients with complete heart block and subacute

TABLE 4.—*Observations in Patients with Chronic Rheumatic Valvular Disease (Cases 8, 9 and 10)*

Date, 1928-1929	Carbon Dioxide Tension		Arteriovenous Difference, per Cent by Volume	Carbon Dioxide Excreted, Cc. per Min.	Cardiac Output, Liters per Minute	Pulse Rate per Minute	Stroke Volume, Cc.	Blood Pressure		Pulse Pressure	Oxygen Used, Cc. per Minute	Respiratory Quotient	Expired Air		Total Ventilation, Liters per Minute	Vital Capacity		Comment
	Alveolar, Mm. Hg.	"Virtual" Venous, Mm. Hg.						Systolic Mm. Hg.	Diastolic Mm. Hg.				Percentage of Oxygen	Percentage of Carbon Dioxide		Cubic Centimeters	Per Cent of Normal	
J. B., a man, aged 52; height, 164 cm.; weight, 66 Kg.; diagnosis, aortic stenosis and insufficiency																		
November 29.....	36.9	45.5	4.04	184	4.6	68	68	110	55	55	265	0.70	4.05	2.81	18	6.5	3,000	70 1 Gm. of digitalis daily
December 7.....	35.2	45.6	4.65	202	4.3	73	60	100	48	52	252	0.80	3.64	2.91	19	6.9	2,800	65 1 Gm. of digitalis daily
S. T., a youth, aged 16; height, 168 cm.; weight, 53.5 Kg.; diagnosis, mitral stenosis and aortic insufficiency (mild)																		
November 3.....	35.1	44.4	4.09	195	4.8	82	58	118	60	58	254	0.77	3.96	3.04	16	6.4	2,800	69 No medication
November 4.....	37.9	46.9	3.86	188	4.9	78	63	115	70	45	245	0.77	4.46	3.42	12	5.5	3,000	73 No medication
I. C., a youth, aged 18; height, 167 cm.; weight, 68.5 Kg.; diagnosis, aortic insufficiency and mitral stenosis and insufficiency (marked)																		
February 9.....	33.4	50.4	4.88	202	4.1	69	61	140	20	120	265	0.77	4.80	3.67	13	5.5	3,400	77 No medication
February 22.....	30.8	53.9	5.59	211	3.8	65	58	142	29	113	273	0.77	4.85	3.74	14	5.6	3,150	71 No medication

rheumatic fever, we found a striking lack of relationship between blood pressure and cardiac output. Reference to table 4 will show that in case 9 the pulse pressure was 52 mm. and the cardiac output 4.9 liters, whereas in case 10 the pulse pressure was 117 mm. and the cardiac output 4 liters a minute. The output of the heart accompanying the higher pulse pressure was almost 1 liter less per minute than that associated with the lower one.

Vital Capacity, Alveolar Carbon Dioxide, Carbon Dioxide of the Expired Air and the Respiratory Minute Ventilation: The vital capacities were lower than those found in the other groups of patients. In spite of the reduced vital capacities, no râles were heard in the lungs, and one patient, whose vital capacity was 73 per cent (case 9), was able to play basketball three times a week. We do not believe that there was any impairment of gaseous diffusion between the blood and the alveolar air. No remarkable variations from normal were observed in the alveolar carbon dioxide tension, the carbon dioxide of the expired air and the respiratory minute volume.

COMMENT

The Output of the Heart per Minute and per Beat.—We have demonstrated that the output of the heart per minute measured by the method used remains within normal limits when the patient is in a compensated condition, even with the added burden of complete heart block, auricular fibrillation, subacute rheumatic fever or chronic rheumatic valvular disease. We did, however, find certain evidence to lead us to believe the output of the heart is decreased with the onset of congestive failure.

Evidence that the Output of the Heart May be Decreased in Congestive failure.—By serial observations we have demonstrated an increase in the cardiac output of four patients with compensated heart disease whose minute output previously had been found to be low. There was no evidence of congestive failure in these patients, three of whom had vital capacities between 91 and 112 per cent of their normal (cases 4, 6 and 7). This increased cardiac output was associated in two patients (cases 5 and 6) with conversion of auricular fibrillation to normal rhythm; in another (case 4), with the abolition of a pulse deficit with digitalis, and in the fourth (case 7), who had subacute rheumatic fever, with improvement following rest in bed. Coincident with this increase in cardiac output, there was an increase in the alveolar carbon dioxide and in the percentage of carbon dioxide in the expired air, and a decrease in the pulmonary minute ventilation.

It has been pointed out by other investigators¹⁷ that in patients with congestive failure there is a decrease in the arterial or alveolar carbon

17. Harrop (footnote 9). Meakins, Dautrebande and Fetter (footnote 4). Peabody (footnote 10). Peters and Barr (footnote 11).

dioxide, and in the percentage of carbon dioxide of the expired air, and an increase in the pulmonary minute ventilation.

Thus, in our patients, when the cardiac output was low, the values of the alveolar carbon dioxide, the percentage of carbon dioxide in the expired air and the pulmonary minute ventilation were changed in the same direction as those reported in patients with cardiac failure. It does not seem unreasonable to infer, then, that the output of the heart is probably decreased in congestive failure. This is contrary to the opinion of some observers, who contend that the cardiac output is increased in congestive failure. The general physiologic disturbances that take place in patients with cardiac decompensation are very complex, however, and too much inference as to what occurs when the heart fails should not be drawn from this small series of patients with compensated heart disease.

SUMMARY

1. The output of the heart was studied in three patients with complete heart block, two of whom were under 25 years of age; in three patients with auricular fibrillation before and after conversion to normal rhythm, two of whom had mitral stenosis; in one patient with subacute rheumatic fever without a definite valvular lesion, and in three patients with chronic rheumatic valvular disease with regular rhythm. The method of Field, Bock, Gildea and Lathrop was used. All patients were in a well compensated condition and the observations were made while the patient was in the basal state.

2. The patients with complete heart block had a minute output of the heart within the range of normal, but each had a greatly increased stroke volume.

3. Of the three patients with auricular fibrillation, the two with mitral stenosis showed an increase in cardiac output of one fourth or more when the rhythm became regular. They did not have a pulse deficit. The cardiac output of one of these patients was the same with the irregularity of auricular fibrillation as with an irregular sino-auricular rhythm caused by auricular premature contractions. When a regular rhythm without premature contractions was established, there was a 29 per cent increase in the cardiac output. The third patient, who had a pulse deficit of from 15 to 20 a minute but no mitral stenosis, showed a corresponding increase in output when the pulse deficit was eliminated with digitalis. No further increase occurred when normal rhythm was established with quinidine sulphate.

4. The cardiac output of the patient with subacute rheumatic fever showed considerable fluctuation but was within normal limits. Clinical improvement in the patient's condition was associated with an increase in the level of cardiac output.

5. The output of the heart in five patients with chronic rheumatic valvular disease associated with regular rhythm was normal.

6. A striking lack of relationship between blood pressure and cardiac output in the same and in different individuals was demonstrated.

7. We have shown an increase in the cardiac output of four patients. Coincident with this increase, there was an increase in the alveolar carbon dioxide, and in the percentage of carbon dioxide of the expired air and a decrease in the respiratory minute ventilation. It was previously shown by other investigators that patients with congestive heart failure have a lowered arterial or alveolar carbon dioxide and percentage of carbon dioxide in the expired air, with an increase in the respiratory minute volume. Then, in our patients, when the cardiac output was low, the values of the alveolar carbon dioxide, the percentage of carbon dioxide of the expired air and the pulmonary minute volume were changed in the same direction as in patients with congestive failure. From these observations, we have suggested that there may be a decrease in the output of the heart with the onset of congestive failure.

THE METABOLISM OF OBESITY

V. MECHANICAL EFFICIENCY *

CHI CHE WANG, PH.D.

SOLOMON STROUSE, M.D.

AND

ZELMA O. MORTON, B.S.

CHICAGO

Previous papers of this series have dealt with the relation of food intake and body weight in obese subjects,¹ basal metabolism,² the specific dynamic action of foods³ and the distribution of energy production after taking food.⁴ The present communication will take up the mechanical efficiency of obese women as compared with that of normal and underweight subjects. Little has been written on this subject. Aside from the studies made on two obese subjects by Jaquet and Svenson,⁵ the only paper which we were able to find having a direct bearing on our work was that reported by Gessler.⁶ Their results will be discussed with ours later.

EXPERIMENTAL WORK

In this investigation forty-one experiments were conducted on twenty-seven obese women varying in weight from 60.9 to 118.6 Kg. (134 to 262 pounds) with a percentage overweight of from 12.2 to

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1. Strouse, Solomon; and Dye, M.: Studies on the Metabolism of Obesity: I. The Relation Between Food Intake and Body Weight in Some Obese Persons, *Arch. Int. Med.* **34**:267 (Sept.) 1924.

2. Strouse, Solomon; Wang, C. C., and Dye, M.: Studies on the Metabolism of Obesity: II. Basal Metabolism, *Arch. Int. Med.* **34**:275 (Sept.) 1924.

3. Wang, Chi Che; Strouse, Solomon, and Saunders, Alice D.: Studies on the Metabolism of Obesity: III. The Specific Dynamic Action of Food, *Arch. Int. Med.* **34**:573 (Oct.) 1924.

4. Wang, Chi Che; Strouse, Solomon, and Saunders, Alice D.: The Metabolism of Obesity: IV. The Distribution of Energy Production After Food, *Arch. Int. Med.* **36**:397 (Sept.) 1925.

5. Jaquet, A., and Svenson, N.: Zur Kenntnis des Stoffwechsels fettstüchtiger Individuen, *Ztschr. f. klin. Med.* **41**:391, 1900.

6. Gessler, von H.: Die Ökonomie der menschlichen Muskelarbeit: II. Mitteilung die Ökonomie bei Fettsucht, *Deutsches Arch. f. klin. Med.* **157**:36 (Sept.) 1927.

110.1 as compared with the standards accepted by life insurance companies.⁷ With the exception of four subjects who were 16, 31, 32 and 56 years of age, the ages of this group ranged between 18 and 28 years. For comparison, the same experiments were conducted on nine normal women between the ages of 19 and 38 and on seven thin women between the ages of 20 and 40. The subjects in the normal group varied in weight from 48.3 to 63.2 Kg. (107 to 140 pounds) with a percentage deviation from the standard of from +8 to -7.9. The underweight subjects weighed from 88 to 113 pounds (40 to 51.3 Kg.) and were from -15.3 to -27.1 per cent underweight.

As in our previous studies of this series,² the Tissot gasometer, with the Haldane gas analysis apparatus was employed for the measurement of the heat production. The work done was measured by a bicycle ergometer designed by C. Drinker of Harvard University. Each subject received a practice period varying in length from fifteen minutes to several hours according to her ability. Many of the obese women had to repeat the practice several times, and a few of them had to give up the test after many unsuccessful attempts.

All the experiments were conducted on subjects who were in a postabsorptive condition. After measuring the heat production of the person while sitting on the ergometer, a second test was taken while she was riding on the machine with a load of about 2.7 Kg. (6 pounds) at a speed of about 120 revolutions per minute, exact values being given in the tables. The duration of the first test was ten minutes, while that of the latter varied from about three to eight minutes, depending on the volume of gas expired. As the capacity of the gasometer bell is limited to about 120 liters, it was impossible in the majority of cases to continue our experiments during exercise much longer than five minutes. For the same reason we were unable to carry our experiments through the recovery period and to determine the "oxygen debt" of our subjects. Nevertheless, our results on the three types of subjects are relative and interesting. The energy spent on muscular work was calculated from the difference in heat production of the two tests and expressed as percentage of mechanical efficiency.

COMMENT

Tables 1, 2 and 3 show that the mechanical efficiency of the three groups varied greatly. In the obese group the mechanical efficiency ranged from 15 to 31.3, with an average of 21.7 per cent. As there seemed to be a general trend to a decrease in mechanical efficiency with

7. Association of Life Insurance Medical Directors and Actuarial Society of America, *Medico Actuarial Mortality Investigation*, 1912.

TABLE 1.—*Mechanical Efficiency of Obese Subjects*

Sub- ject	Age, Yrs.	Height, Cm.	Weight		Heat Production per Hour in Calories			Work Done, Cal- ories	Mechan- ical Ef- ficiency, per Cent
			Kilo- grams	Percentage Deviation from Normal	Sitting on Er- gometer	Exer- cising	Energy Spent on Work		
A. L.....	26	152.1	112.7	+110.1	119	386	268	46.7	17.5
A. L.....	26	151.5	104.8	+ 97.0	92	362	269	40.3	15.0
A. L.....	26	151.4	101.0	+ 88.4	97	342	245	38.5	15.7
H. B.....	18	175.3	118.6	+ 85.1	106	379	274	55.4	20.3
A. L.....	26	151.4	98.9	+ 84.4	93	351	259	46.9	18.1
H. B.....	18	175.5	118.5	+ 84.3	101	365	263	51.0	19.4
S. L.....	32	145.0	92.6	+ 77.2	78	417	340	79.4	23.4
E. B.....	16	156.9	91.7	+ 73.9	105	349	244	43.7	17.9
E. H.....	30	168.4	111.1	+ 73.4	80	343	263	49.0	22.4
M. C.....	21	161.9	98.4	+ 73.2	78	313	235	48.2	20.5
E. H.....	31	168.1	110.2	+ 73.2	81	326	245	52.6	21.5
P. M.....	18	163.8	96.8	+ 73.2	85	248	163	43.5	26.8
C. G.....	27	164.5	101.8	+ 69.7	77	259	182	43.1	23.7
E. B.....	16	157.2	89.1	+ 67.5	109	308	199	46.4	23.3
C. G.....	27	164.5	99.6	+ 65.9	69	246	177	41.5	23.4
E. H.....	31	167.9	105.4	+ 65.6	148	321	173	37.7	21.7
L. K.....	29	151.6	87.3	+ 62.7	77	351	274	51.8	19.0
E. B.....	17	157.7	84.8	+ 59.4	90	318	228	36.4	16.0
E. B.....	17	157.7	83.4	+ 56.8	101	302	201	46.2	23.0
M. C.....	19	161.5	85.9	+ 54.9	84	320	236	56.6	24.0
M. B.....	19	167.3	90.4	+ 50.7	93	299	206	36.8	17.9
M. P.....	19	165.4	86.0	+ 50.2	79	302	222	44.6	20.1
I. B.....	21	161.6	85.7	+ 50.0	75	261	186	47.5	25.5
D. M.....	24	163.5	85.5	+ 49.2	86	262	177	51.4	29.1
P. F.....	18	159.1	80.7	+ 49.1	69	242	173	42.3	24.4
P. K.....	21	161.6	84.2	+ 48.2	60	300	240	51.0	21.2
E. F2.....	23	166.1	85.7	+ 45.0	69	322	253	51.8	20.5
K. Y.....	19	160.8	78.5	+ 44.0	67	308	241	47.3	19.6
D. L.....	19	161.3	78.6	+ 41.8	77	253	176	47.3	27.0
B. H2.....	29	159.1	79.0	+ 39.0	80	362	282	54.6	19.4
E. F1.....	19	154.9	71.4	+ 37.7	64	295	230	48.3	21.0
P. M.....	19	165.1	78.4	+ 36.9	81	296	216	44.5	20.6
B. H2.....	28	159.1	76.7	+ 35.0	77	245	168	50.2	29.9
V. C.....	21	166.1	79.6	+ 34.6	70	295	225	51.8	23.0
K. V.....	19	160.5	71.1	+ 30.4	81	321	241	44.5	18.5
E. R.....	36	151.4	69.2	+ 23.7	61	309	248	56.2	22.7
B. H1.....	23	168.3	72.3	+ 19.5	71	299	229	42.8	18.7
I. R.....	56	154.4	72.0	+ 17.3	59	299	240	49.3	20.5
F. M.....	26	152.7	60.9	+ 13.6	62	183	117	35.4	30.3
B. R.....	20	156.7	61.3	+ 13.3	72	286	214	50.2	23.4
T. A.....	22	160.0	62.7	+ 12.2	57	197	140	43.9	31.3
Average ...	24.4	160.1	86.0	+ 51.3	82.2	301.6	222.9	45.9	21.7

TABLE 2.—*Mechanical Efficiency of Normal Subjects*

Sub- ject	Age, Yrs.	Height, Cm.	Weight		Heat Production per Hour in Calories			Work Done, Cal- ories	Mechan- ical Ef- ficiency, per Cent
			Kilo- grams	Percentage Deviation from Normal	Sitting on Er- gometer	Exer- cising	Energy Spent on Work		
E. B.....	24	161.8	61.4	+8.0	64	302	238	53.1	22.3
D. T.....	20	153.4	56.2	+6.6	58	263	205	51.0	24.9
N. H.....	21	161.0	58.8	+4.2	54	268	214	50.5	23.6
E. M.....	19	163.3	57.3	+1.6	63	261	298	55.2	27.9
E. G.....	19	160.7	53.6	—2.5	60	293	233	54.8	23.5
P. D.....	38	153.4	55.0	—3.2	58	328	270	57.0	21.1
V. A.....	27	151.1	49.9	—6.2	54	266	212	54.1	25.5
E. S.....	19	154.9	48.3	—6.8	61	268	207	56.1	27.1
J. W.....	35	172.1	63.2	—7.9	70	264	194	45.8	23.6
Average ...	24.6	159.0	55.9	—0.69	60	268	219	53.1	24.4

an increase of obesity, this group was subdivided arbitrarily into four divisions according to the degree of obesity. It can be seen clearly from table 4 that the most obese group, which ranged between 110.1 and 84.3 per cent overweight, gave an average mechanical efficiency of 17.7 per cent, and the value increased gradually in the next three divisions. The subjects in the last group, ranging from 23.7 to 12.2 per

TABLE 3.—*Mechanical Efficiency of Underweight Subjects*

Sub- ject	Age, Yrs.	Height, Cm.	Weight		Heat Production per Hour in Calories			Work Done, Cal- ories	Mechan- ical Ef- ficiency, per Cent
			Kilo- grams	Percentage Deviation from Normal	Sitting on Er- gometer	Exer- cising	Energy Spent on Work		
C. S.....	21	162.3	48.6	— 15.1	61	264	203	53.4	26.3
O. D.....	25	158.2	45.4	—18.9	51	256	205	54.1	26.4
M. C.....	25	159.0	44.1	—21.8	57	273	216	63.1	29.2
V. S.....	20	156.2	40.0	—25.4	57	250	193	49.2	25.5
V. P.....	25	159.0	41.5	—26.4	66	281	215	58.5	27.2
M. S.....	21	169.9	45.6	—27.0	55	217	162	44.7	27.6
M. R. W...	40	169.6	51.3	—27.1	58	200	142	53.9	30.9
Average ...	25	162.0	45.2	—23.1	57.9	248.7	190.9	52.4	27.6

TABLE 4.—*Average Mechanical Efficiency of Obese, Normal and Underweight Subjects*

Age, Years	Height, Cm.	Weight		Range of Per- centage Over- weight	Heat Production per Hour in Calories					Mechan- ical Effi- ciency, per Cent	
		Kilo- grams	Percentage Deviation from Normal		Sitting on the Ergometer			Exer- cising	Energy Spent on Work		Work Done, Cal- ories
					Total	Per Kilo- gram					
Obese											
23.3	159.5	109.1	+91.6	110.1—84.3	100	0.92	361	263	46.5	17.7	
23.0	161.2	94.2	+64.6	77.2—50.0	88	0.94	311	232	47.3	21.8	
21.6	161.4	79.1	+40.9	50.0—30.0	73	0.93	292	219	45.0	22.9	
30.5	157.2	66.4	+16.6	23.7—12.2	64	0.96	262	198	46.3	24.5	
Normal											
24.6	159.0	55.9	— 0.69+	8.0 to — 7.9	60	1.07	268	219	53.1	24.4	
Underweight											
25.0	162.0	45.2	—23.1	—15.1 to —23.7	58	1.28	249	181	52.4	57.6	

cent overweight, gave an average mechanical efficiency of 24.5 per cent, which was almost identical with that found in the normal group. The percentage deviation from the standard weight of the subjects in the normal group varied from +8 to —7.9, and their mechanical efficiency ranged from 21.1 to 27.9 per cent. The subjects in the underweight group gave the highest mechanical efficiency with a range of from 25.5 to 30.9 with an average value of 27.6 per cent.

In comparing our results with those of other investigators, the average value of our normal group agreed with that reported by

Loewy,⁸ who stated that for a well trained man turning a brake ergometer the average net efficiency would be between 24 and 25 per cent. However, these values are much lower than those given by Benedict and Cathcart,⁹ who gave from 28 to 30 per cent as an average drawn from a large series of experiments on men. This discrepancy was probably due in part to the fact that their subjects being men were more muscular and were more familiar with the ergometer than our subjects who were all women. This statement was substantiated by the higher results obtained in our undernourished group, many of whom were well acquainted with bicycle riding and were more muscular than the members of the other two groups. The average value from this group was 27.6 per cent. Our results on obesity did not agree with Loewy's statement that the energy consumption per kilogrammeter of work varied inversely with the body weight. This difference may be due in part to the fact that the increased weight of our subjects came largely from inert fat, whereas in his case it was largely due to an increase of muscles. Jaquet and Svenson,⁵ using a special pedal apparatus, found that the values of the increased oxygen consumptions (cubic centimeters per minute) per kilogrammeter of work of two obese women were 4.67 and 1.87 (average of three tests). These values were higher than those found by Katzenstein¹⁰ in his study on four subjects with an oxygen consumption of 1.187, 1.244, 1.435 and 1.504 cc. In a study made on thirteen normal and eight obese subjects, Gessler⁶ demonstrated that the subjects in the obese group used less oxygen than those in the normal group in performing the same piece of work which was measured by a special piece of hand apparatus. All his subjects were thoroughly trained before starting the investigation. This might account for the discrepancy between his results and ours. His work further showed that mechanical efficiency varied with age in both the obese and the normal subjects. Thus the age of the subjects in the obese group varied from 16 to 40 years with a mechanical efficiency of from 18.2 to 28.1 per cent. The corresponding values of the normal group were 17 to 44 years and 15.2 to 23.5 per cent. Table 5 gives the results of our experiments arranged according to age. No correlation with age was found in either the obese or the normal group. However, his conclusions were substantiated by our under-

8. Loewy, A.: Der respiratorische und der Gesamtumsatz: IX. Der Nutzeffekt der Umsatzsteigerung bei Muskelarbeit, in Oppenheimer: Handbuch der Biochemie, Jena, 1911, vol. 4, p. 274.

9. Benedict, Francis G., and Cathcart, Edward P.: Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, Carnegie Institution of Washington, 1913.

10. Katzenstein, George: Zusammenstellung der Gehversuche von Zimm, Arch. f. d. ges. Physiol. 49:368, 1891.

TABLE 5.—*Relation of Mechanical Efficiency to Age*

Subject	Age, Years	Weight		Work Done, Calories	Mechanical Efficiency, per Cent
		Kilo- gram	Percentage Above Normal		
Obese					
E. B.....	16	91.7	73.9	43.7	17.9
E. B.....	16	89.1	67.5	46.4	23.3
E. B.....	17	84.8	59.4	36.4	16.0
E. B.....	17	83.4	56.8	46.2	23.0
H. B.....	18	118.6	85.1	55.4	20.3
H. B.....	18	118.5	84.3	51.0	19.4
P. M.....	18	96.0	73.2	43.5	26.8
P. F.....	18	80.7	49.1	42.3	24.4
M. C.....	19	85.9	54.9	56.6	24.0
M. B.....	19	90.4	50.7	36.8	17.9
M. P.....	19	86.0	50.2	44.6	20.1
R. V.....	19	78.5	44.0	47.3	19.6
D. L.....	19	78.6	41.8	47.3	27.0
E. FL.....	19	71.4	37.7	48.3	21.0
P. M.....	19	78.4	36.9	44.5	20.6
K. V.....	19	71.1	30.4	44.5	18.5
B. R.....	20	61.3	13.3	50.2	23.4
M. C.....	21	98.4	73.2	48.2	20.5
I. B.....	21	85.7	50.0	47.5	25.5
P. K.....	21	84.2	48.2	51.0	21.2
V. C.....	21	79.6	34.6	51.8	23.0
I. A.....	22	62.7	12.2	43.9	31.3
E. F2.....	31	105.4	65.6	37.7	21.7
B. H1.....	23	72.3	19.5	42.8	18.7
D. M.....	24	85.5	49.2	51.4	29.1
A. L.....	26	112.7	110.1	46.7	17.5
A. L.....	26	104.8	97.0	40.3	15.0
A. L.....	26	101.0	88.4	38.5	15.7
A. L.....	26	98.9	84.4	46.9	18.1
F. M.....	26	60.9	13.6	35.4	30.3
C. G.....	27	101.8	69.7	43.1	23.7
C. G.....	27	99.6	65.9	41.5	23.4
B. H2.....	28	76.7	35.0	50.2	29.0
L. K.....	29	87.3	62.7	51.8	19.0
B. H2.....	29	79.0	39.0	54.6	19.4
E. H.....	30	111.1	73.4	49.0	22.4
E. H.....	31	110.2	73.2	52.6	21.5
E. H.....	31	105.4	65.6	37.7	21.7
S. L.....	32	92.6	77.2	79.4	23.4
E. R.....	36	69.2	23.7	56.2	22.7
I. R.....	56	72.0	17.3	49.3	20.5
Weight					
Subject	Age, Years	Kilo- gram	Percentage Deviation from Normal	Work Done, Calories	Mechanical Efficiency, per Cent
			Normal		
E. M.....	19	57.3	+1.6	55.2	27.9
E. G.....	19	53.6	-2.5	54.8	23.5
E. S.....	19	48.3	-6.8	56.1	27.1
D. T.....	20	56.2	+6.6	51.0	24.9
N. H.....	21	58.8	+4.2	50.5	23.6
E. B.....	24	61.4	+8.0	53.1	22.3
V. A.....	27	49.9	-6.2	54.1	25.5
J. W.....	35	63.2	-7.9	45.8	23.6
D. P.....	38	55.0	-3.2	57.0	21.1
Underweight					
V. S.....	20	40.0	-25.4	49.2	25.5
C. S.....	21	48.6	-15.1	53.4	26.3
M. S.....	21	45.6	-27.0	44.7	27.6
O. D.....	25	45.4	-18.9	54.1	26.4
V. P.....	25	41.5	-26.4	58.5	27.2
M. C.....	25	44.1	-21.8	63.1	29.2
M. R. W.....	40	51.3	-27.1	43.9	30.9

nourished group in which the subjects varied in age from 20 to 40 years and gave a mechanical efficiency of from 25.5 to 30.9 per cent.

It was of interest to note that the energy expenditure for sitting on the ergometer was higher in the obese subjects than in those of the other two groups. Thus the values of the four divisions of the obese group as shown in table 4 were 100.1, 88.2, 73.2 and 63.6 calories per hour. The corresponding values for the normal and underweight group were 60 and 57.9, respectively. The higher values of the obese group were undoubtedly due to the increased load of these subjects as shown by the average energy expenditure per kilogram of body weight. These values were 0.913, 0.936, 0.925 and 0.956 for the obese group and 1.072 and 1.279 calories for the normal and underweight groups.

SUMMARY

A total of fifty-seven experiments were conducted on twenty-seven obese, nine normal and seven underweight subjects.

The mechanical efficiency varied inversely with the percentage overweight. The average values for the three groups were 21.7, 24.4 and 27.6 per cent. A gradual decrease in mechanical efficiency with an increase in obesity was observed in the obese group.

No relation was noted between the mechanical efficiency and the age of the subject.

An increase of obesity was accompanied by an augmentation of heat production with the subject sitting on the ergometer.

LIPOID NEPHROSIS

REPORT OF A CASE OF UNUSUAL DURATION *

EATON M. MACKAY, M.D.

AND

CHRISTOPHER JOHNSTON, M.D.

NEW YORK

The literature abounds with reports of cases of chronic nephrosis; observations on the clinical manifestations of the disease, its course, its frequent termination by peritonitis and its pathology are not uncommon. We have not, however, been able to find a report of a case that has lasted so many years as the one herein discussed. According to Munk,¹ the disease may last months or years. Clausen² reported a case in a child, aged 13, who had had the disease since early childhood and was still living in 1924, and Lowenthal³ reported a fatal case that lasted for nearly four years. The duration of other fatal cases has, in general, not been so long as this. In Davison and Salinger's⁴ series, the longest fatal case lasted thirty-six months; one of Kaufmann and Mason's⁵ patients lived thirty-one months, and one of Volhard and Fahr's⁶ lived fourteen months.

Our patient was under observation for six years, and the history, which we feel is reliable, gives further evidence that the duration of the disease was at least seventeen years.

REPORT OF CASE

History.—M. M., a Jewish boy, was born on March 18, 1909, and died on Dec. 2, 1928. The family history is noncontributory. The patient was appar-

* Submitted for publication, Nov. 14, 1929.

* From the Hospital of the Rockefeller Institute for Medical Research.

* Through the courtesy of the Beth David Hospital and the Fifth Avenue Hospital, we were able to consult their original records of this patient.

1. Munk, F.: *Die Nephrosen*, Med. Klin. **39**:41, 1916.

2. Clausen, S. W.: *Parenchymatous Nephritis*, Am. J. Dis. Child. **29**:587 (May) 1925.

3. Lowenthal, K.: *Zur Frage der Lipoid Nephrose*, Virchows Arch. f. path. Anat. **261**:109, 1926.

4. Davison, W. C., and Salinger, R.: *Tubular Nephritis (Nephrosis) in Children and Its Relationship to Other Forms of Nephritis*, Bull. Johns Hopkins Hosp. **41**:329, 1927.

5. Kaufmann, J., and Mason, E.: *Nephrosis: A Clinical and Pathologic Study*, Arch. Int. Med. **35**:561 (May) 1925.

6. Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

ently normal at birth. He had measles at 9 months, with uneventful recovery. He gave no history of any other disease, except as noted under present illness.

Present Illness.—When he was about 16 months old, his face and cheeks became swollen, and in a few months his lower extremities started to swell. He was admitted to the Harlem Hospital for treatment for kidney disease, but was discharged unimproved. (Records of this admission are not available.) He was put on a diet in which salt, meat, eggs, pepper and spicy foods were prohibited, and was kept on this diet until he was 15 years old.

According to his mother, his urine always contained large quantities of albumin, and since the first attack he suffered from marked edema of the face, abdomen and legs at least every year, and usually oftener. The edema generally lasted but two or three weeks.

Records from the Beth David Hospital show that he was readmitted on Nov. 4, 1922 (previous records destroyed by fire) with marked edema of both legs and puffiness of the eyelids. His blood pressure was 118 systolic and 72 diastolic, his heart was normal, the lungs clear and the pharynx without injection. The patient was discharged against advice on Nov. 11, 1922.

He was readmitted on Feb. 1, 1923, with edema of the face, vomiting and resolving pneumonia of the right lower lobe. Recovery was rapid. The patient was discharged on February 11.

On July 2, 1923, his tonsils and adenoids were removed. On July 28, he was admitted with appendicitis, and at operation, pus was found in the abdominal cavity. No culture was taken. No edema was observed on admission, but on August 11, some puffiness appeared about the eyelids and soon became generalized. He apparently made a good recovery following operation and was discharged with edema on Sept. 5, 1923.

On June 1, 1925, he awakened with edema of the eyelids, and four days later was admitted to the Beth David Hospital with marked edema of the eyelids and ascites. Special examination of the optic fundi showed no changes. By July 3, there was edema of the eyelids and over the sacrum and lower extremities; marked scrotal edema had developed, and the ascites had increased. Subjectively, the patient was well. There was slight improvement after this, but he was discharged against advice on Sept. 29, 1925, with considerable edema. Various therapeutic measures had been tried. Hot packs were without effect, and there was no apparent benefit from thyroid extract in doses of from 0.05 Gm. daily, beginning June 12 and gradually increasing, to 1 Gm. daily by August 3. Daily injections of merbaphen between September 17 and 21 were without effect.

He remained at home in bed until Feb. 12, 1926, when he was admitted to the Fifth Avenue Hospital on account of massive edema of the extremities. On February 16, almost a gallon of ascitic fluid was obtained. Hot packs were tried, but were discontinued on February 25, when he developed bronchopneumonia. Recovery was uneventful. The patient was discharged improved but with considerable edema on May 8.

He returned to the Fifth Avenue Hospital on Oct. 4, 1926. He had not been out of bed since his discharge in May, and the swelling had varied somewhat, but was always pronounced. On admission, the blood pressure was 105 systolic and 65 diastolic. The optic fundi were pale, but otherwise normal. There was marked edema below the knees, and the abdomen was tense with fluid. He was given digitalis and thyroid extract (one tablet three times a day) throughout his stay, and was kept on a high protein, salt-free diet. On October 13, he was

given a transfusion of 400 cc. of blood, and on October 29 some small tonsillar tags were removed under local anesthesia. He was discharged improved, but still considerably edematous, on Nov. 15, 1926.

The patient remained at home in bed, feeling fairly well. His appetite was fair. He had no shortness of breath. The swelling remained unaltered for the most part. He was readmitted to the Fifth Avenue Hospital on Aug. 30, 1927, on account of the edema. He was pale and poorly nourished. The lower extremities were still extremely edematous and on September 1, 7 liters of

TABLE 1.—*Urinalyses in Case, from Records of Both David and Fifth Avenue Hospitals*

Date	Specific Gravity	Albumin	Casts	White Blood Cells and Epithelial Cells	Red Blood Cells	Remarks
11/ 5/22	1.025	Positive	0	0	0	These analyses were recorded during a time when the patient was markedly edematous, according to the clinical notes. It is not known whether the sediments were examined in freshly voided specimens
11/ 7/22	1.028	Positive	0	Few	0	
11/ 9/22	1.030	Positive	Granular	0	0	
11/10/22	1.025	Positive	0	0	0	
2/ 4/23	1.018	Negative	0	0	0	Clinical notes: "resolving" pneumonia; edema of face
7/30/23	1.025	Negative	0	Few	0	During peritonitis; "patient considerably edematous"
8/20/23	1.020	Trace	0	Few	0	
6/11/25 to 9/23/25	1.024 to 1.032	8 Gm. / L. and +++	Few granular, few white blood cell, few hyaline	Few to moderate	None, except on Aug. 31; then occasional ones; Sept. 2, moderate	Concentration test June 17: specific gravity 1.024 to 1.034
2/12/26 to 3/18/26	3 to 12 Gm./L., generally 8 to 9	Moderate hyaline, moderate granular	Few	None	Feb. 20; specific gravity 1.028 to 1.038
10/ 4/26 to 11/15/26	1.014 to 1.019	4 to 10 Gm./L., generally 8 to 9	Heavy hyaline, Many finely granular	+	0	Oct. 8; specific gravity 1.013 to 1.015, which is possibly inaccurate owing to edema fluid
8/30/27 to 11/10/27	1.010 to 1.015	6 to 7 Gm./L.	Hyaline +; granular +	Few	Few noted in 2 exam- inations	Concentration test: specific gravity 1.021 to 1.023

ascitic fluid was withdrawn. Liver diet and manganese were given without effect on the anemia and on October 21 the patient received a transfusion of 500 cc. of blood.

On Nov. 10, he was transferred to the Hospital of the Rockefeller Institute. According to his statement, at the time his legs were less than a third of their former size, and there had been a general decrease of the edema during the preceding six months.

Physical Examination (by Dr. E. M. Mackay).—The general appearance was that of an undernourished boy of from 10 to 12 years of age, while the actual age was 18 years. The skin was pasty and sallow. The head was normal in shape. The ears presented no inflammation. The eyes were normal. In the mouth and pharynx, the mucosa was pale, and the teeth were in poor condition. The pharynx did not show injection. The thyroid gland was not palpable.

There was a marked outward flare of the lower part of the thoracic cage, probably as a result of the ascites. The diaphragm was evidently considerably elevated. No abnormal sounds were heard over the lungs. The maximum impulse of the heart was palpable in the fourth space 9 cm. to the left of the midline. Dulness extended 5 cm. to the right, and 8 cm. to the left, in the fourth space. Sounds were clear; no murmurs were heard. The radial pulses were equal and regular; the vessel walls were soft. Blood pressure was 108 systolic and 78 diastolic. The abdomen was greatly distended from ascites. Numerous striae were present. None of the organs could be palpated. The genitalia were normal. There was first degree edema of the feet and ankles. The reflexes were normal.

TABLE 2.—Data Obtained from Records of Previous Admissions to Beth David and Fifth Avenue Hospitals: Blood Chemistry and Phenolsulphonphthalein Tests

Date	Urea Nitrogen, Mg. per 100 Cc.*	Chlorides	Cholesterol*	Hemoglobin, per Cent	Red Blood Cells, Millions	Phenolsulphonphthalein		Excretion Total
						First Hour	Second Hour	
8/25/23	306	80	8.68
1/23/25	0.57	180	40
2/ 3/25	12.0	56
6/13/25	75	4.82	8	12	20
6/15/25	12	25	37
6/18/25	25.0	0.40	220	80
7/ 1/25	12.0	210
7/10/25	25	18	43
7/21/25	12	0.52	...	65	4.00
8/ 1/25	14	0.54	...	78	4.72
8/ 4/25	35	16	51
9/ 1/25	14	0.54	...	80	5.75	30	17	47
9/ 8/25	78	32	14	46
9/10/25	12	0.52	230
9/21/25	32	20	52
2/12/26	22.0	0.57	206	70	5.0	16.6	25	41.6
2/15/26	86	4.8
3/ 4/26	9.0	0.40	...	96	5.1
10/ 4/26	25.0	77	3.75
10/13/26	18.0	280	60	3.21
11/ 2/26	69	3.58	15	20	35
8/31/27	14.0	34	3.1
9/ 1/27	34	3.8	15.3	6.7	22
9/ 2/27	20	19	39
9/ 6/27	30	1.92
10/22/27	55	4.00
10/31/27	58	4.10

* During observation at the Rockefeller Hospital the blood urea nitrogen was never above 15 mg. per 100 cc. The cholesterol varied between 167 and 510, and was generally above 300 mg. per 100 cc.

There was definite, though slight, impairment of the renal function, as shown on the chart, anemia, and the low plasma albumin concentration characteristic of nephrosis. Teleoroentgenographic measurements of cardiac outline showed median right 4 cm., median left 5.5 cm. The total internal diameter of the thorax was 26.5 cm. The results of a quantitative study of the sediment of the urine by the method of Addis⁷ were in entire agreement with the diagnosis of nephrosis. The Wassermann test was negative.

He was placed on a low salt diet with 70 Gm. of protein daily, and there was a gradual decrease of edema as shown by the weight curve. Urea, in a dosage of from 10 to 20 Gm. daily, was given during the latter part of December, and intermittently thereafter. In February, 1928, the basal metabolism was found to be —18.

7. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, *J. Clin. Investigation* 2:409, 1926.

There was a gradual diminution in the amount of edema over a period of several months. In September, a general examination revealed the following features: (1) marked pallor; (2) firm, nonpitting swelling of both ankles; (3) slight clubbing of toes; (4) no enlarged lymph nodes, except at the angle of the jaw; (5) optic fundi pale, but otherwise normal; (6) few remaining teeth in good condition; (7) pharynx clear; (8) thyroid not palpable; (9) lungs clear, bases descending 4 cm. on deep inspiration; (10) relative cardiac dullness normal; heart sounds of good quality, soft systolic murmur over apex, not transmitted, and well marked sinus arrhythmia; (11) liver, soft, smooth and palpable just below the costal margin on deep inspiration; (12) no evidence of ascites; (13) spleen not palpable; (14) slight genital hypoplasia.

He was discharged on September 29, vastly improved, and remained at home with his activities much reduced, but was readmitted on Nov. 6, 1928, because of increasing edema of the legs. In addition to the edema, examination revealed occasional scattered râles in both sides of the chest. The liver edge was palpable on deep inspiration, and the spleen was indefinitely felt on deep palpation.

TABLE 3.—*Results of Tests (Addis) of Sediment of Twelve-Hour Urine*

Date	Volume	Specific Gravity	Red Blood Cells	White Blood Cells and Epithelial Cells	Casts	Differential Count of Casts			
						Hyaline	Epithelial	Granular	Fatty
12/ 1/27	380	1.019	152,000	10,082,000	1,976,000	60	20	20	0
12/30/27	480	1.017	393,600	8,816,000	2,304,000	80	0	4	16
2/ 6/28	380	1.020	144,000	3,344,000	1,672,000	65	0	0	35
3/31/28	680	1.018	136,000	4,080,000	2,584,000	10	0	0	90
5/ 2/28	775	1.019	310,000	6,820,000	1,860,000	70	10	0	20
6/23/28	740	1.016	444,000	3,000,000	1,184,000	100	0	0	0
7/14/28	660	1.015	264,000	4,224,000	704,000	100	0	0	0
7/30/28	655	1.013	786,000	2,358,000	2,538,000	100	0	0	0
9/14/28	684	1.014	68,400	252,000	189,000	76	0	24	0
9/25/28	665	1.014	349,000	900,000	1,970,000	88	0	12	0
11/ 8/28	395	1.015	1,085,000	3,060,000	1,930,000	100	0	0	0

At 8 p. m. on November 27, the patient had a chill, followed by a febrile rise to 105.6. Examination disclosed only slight tenderness along the left side of the abdomen. By the next morning, the abdominal pain had become generalized, and the temperature remained at 105.4. A diagnosis of general peritonitis was made. Operation was not performed, but on December 1 abdominal paracentesis yielded a thin, milky-looking fluid in which were many gram-positive cocci. Culture disclosed a pure culture of hemolytic streptococci.

The patient died on December 2, on the seventh day of the acute illness.

COMMENT

It is unfortunate that the early records of this case cannot be traced. Nevertheless, the history as given here agrees in its essentials with histories obtained from the patient's mother at both the Beth David and the Fifth Avenue Hospitals, except that on one occasion the age of onset was given as 4 years. The story of recurring periods of edema and of the constant (?) presence of albuminuria is common to all the records, and in view of the course of the disease, the absence of hypertension, the later clinical picture and the observations at autopsy, it would be difficult to imagine that the earlier attacks were due to

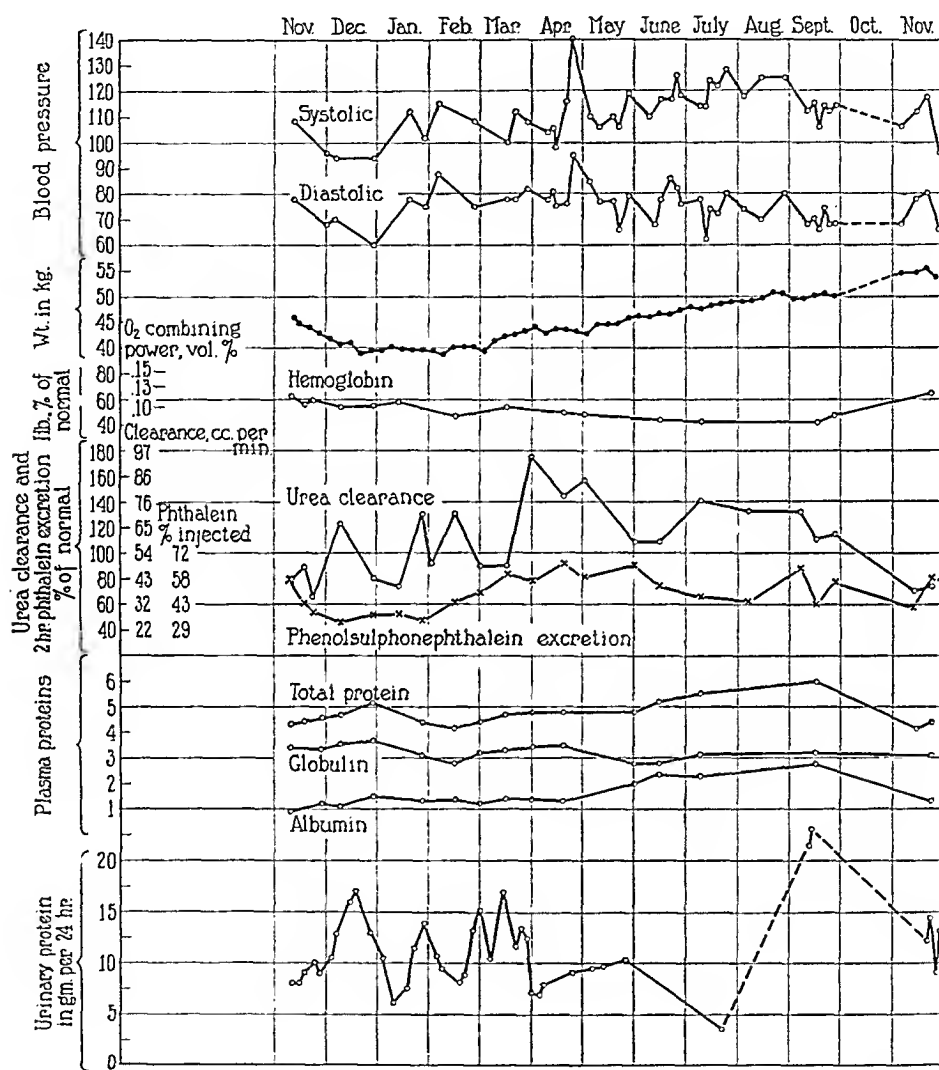
glomerulonephritis. Furthermore, the records of the examinations of the urine show that albuminuria was constant, except at two observations, both of which may be doubted because the clinical notes state clearly that edema was present. Rare red blood cells were said to have been seen on only four occasions in the many examinations made. The urine was not examined for doubly refractile lipoid bodies prior to November, 1927, but they were found present in large numbers on every examination thereafter.

The treatment of this patient is not without interest. From the onset of the disease until March, 1926, when he was 15 years old, he was on a low protein diet. The change to high protein diet at this time was without demonstrable effect, but as we do not know how much the protein intake was restricted, nor how much it was later increased, conclusions are not justified. During the last year of the patient's life, the edema decreased while he was on a high protein diet (120 Gm. daily), but urea was given successfully as a diuretic at the same time, and the plasma albumin did not increase until the daily loss of protein in the urine had decreased somewhat. Thyroid extract was tried repeatedly and in doses up to 1 Gm. daily without effect. Merbaphen, theobromine sodium salicylate, digitalis, calcium chloride, pituitary extract and urea were tried repeatedly. On one occasion, a diuresis started coincident with digitalis medication, and the good effect of urea and of calcium chloride on the urine output was definite. Other medication was entirely without effect.

Foci of infection were sought for, and the records showed that the tonsils and adenoids were removed in July, 1923, October, 1926, and April, 1928. No focus was ever found in the paranasal sinuses. The teeth were badly decayed and were removed one by one until few remained at the time of death. The patient recovered completely from an attack of pneumonia in 1923, and bronchopneumonia in 1925. At an operation for appendicitis in 1923, pus was found in the abdominal cavity. There was no apparent relationship between any of these infections and the course of the disease.

The general development of the patient, it has already been noted, was not commensurate with the actual age. The general bodily conformation and the secondary sex characteristics were those of a boy of from 12 to 14 years of age. This is not remarkable in view of the fact that for almost the first fifteen years of life his diet must have been greatly deficient in protein, and the developmental delay cannot in this case be considered as a specific effect of the disease, as is thought to be the case in examples of so-called renal dwarfism. Furthermore, x-ray pictures showed that in our patient, the skeletal development was normal for his age.

Although anemina is not ordinarily encountered in nephrosis, reference to the tables shows that our patient had a secondary anemia which was at first only slight, but which gradually became more severe. It is especially to be noted that although the erythrocytes occasionally fell to low levels, there was, in general, no indication of deficient erythropoiesis in spite of the two factors of disease and prolonged restricted



Graphic record of the weight and the results in examinations of the blood and the urine of a patient with lipid nephrosis.

diet during the period of growth. During his stay in the Rockefeller Hospital, the hemoglobin showed a steady decline in spite of a high protein diet including eggs, and the additional administration from March 5 to May 19, 1928, of six vials of liver extract daily, representing 600 Gm. of fresh liver. The red count increased from 4,030,000 to 4,800,000 while the patient was receiving liver extract, but in September, four months after its discontinuance, and at a time when the hemoglobin

values were lowest, the red count was found to vary from 4,950,000 to 5,600,000. These latter determinations were checked by two observers, using different pipets and counting chambers and taking blood from either the finger or the ear. The increase in hemoglobin between September and November, 1928, is attributed to the use of pills of ferrous carbonate, U. S. P. (0.3 Gm. three times daily) from September 14 to 28 and from November 6 to 28, and was accompanied clinically by a definite improvement in the patient's color.

There has been much discussion, especially in the German literature, over the question of the secondarily contracted kidney of nephrosis (Munk;⁸ Lowenthal;³ Volhard and Fahr⁶), and it has apparently been established that such cases do occur. We wish merely to call attention to the fact that in this case of such long duration, there was no clinical evidence of secondary contraction of the kidney, as there was no accompanying hypertension, cardiac enlargement or retention of nitrogen.

It is likely that a great many cases reported as "pure nephrosis" are in reality cases of glomerulonephritis accompanied by great tubular degeneration, edema, low plasma proteins and the other signs of nephrosis, and distinguished from pure nephrosis only by the presence of slight hematuria. Addis⁷ showed that normal persons may excrete as many as 425,000 erythrocytes in the urine in twelve hours, and did not consider any count as significant of glomerulonephritis unless the excretion is above 1,000,000. In eleven such counts of the sediment of the urine in this case, none of them gave any evidence that there was any glomerular lesion. Furthermore, the phenolsuphonphthalein tests showed no great reduction in function, and what is perhaps of even greater significance, the test for blood urea clearance showed that this was never greatly depressed below the low normal value of 80 per cent, and was for most of the time well above normal.

8. Munk, F.: Zur Pathogenese der nephrotischen Schrumpfnieren, *Virchows Arch. f. path. Anat.* **226**:81, 1919.

HAY-FEVER

THE IMPORTANCE OF SUBSTANCES OTHER THAN POLLEN IN THE
ETIOLOGY; THEIR INFLUENCE ON SEASONAL CURE *

MILTON B. COHEN, M.D.

AND

J. A. RUDOLPH, M.D.

CLEVELAND

In spite of the advances in the preparation of potent pollen extracts and in the methods of their administration, there are still patients with hay-fever who get practically no relief from their symptoms following preseasonal treatment. The percentage of patients in this group varies from 5 to 10. All others fall into two classes which are about equal in number; namely, those who get complete relief and those in whom marked relief is obtained.

While the use of filtered air¹ in addition for a few hours a day makes complete relief practical for the patients in the partially relieved group, and produces marked relief even in those who were previously in the total failure group, intensive study has shown that many in these two classifications can be transferred to the complete relief group by attention to various factors that have been pointed out before but are not generally stressed.

In 1928, one of us (M. B. C.²) listed the causes for failure as follows: (1) incorrect diagnosis, (2) inadequate or improper treatment, (3) inability of the patient's body to develop a tolerance to pollen following injections of pollen extract and (4) contact with unusually large doses of pollen.

In discussing incorrect diagnosis, it was stated that "Sometimes there is a coexisting sensitivity to some substance other than the pollen which may exacerbate the symptoms during the hay-fever season." Further consideration of this point has led us to the belief that failure to discover and eliminate these extra factors has been responsible for the majority of failures to obtain relief by specific methods.

* Submitted for publication, Oct. 10, 1929.

* From the Asthma and Hay Fever Clinic.

1. Cohen, Milton B.: Further Observations on the Use of Filtered Air in the Diagnosis and Treatment of Allergic Conditions, *J. Lab. & Clin. Med.* **13**:963 (July) 1928.

2. Cohen, Milton B.; Reicher, Jacob, and Breitbart, Joseph: The Causes of Failure in the Treatment of Hay Fever, *Ohio State M. J.* **24**:452 (May) 1928.

Both Vaughan ³ and Balyeat ⁴ discussed some of these factors. The latter, particularly, has reported a study of 719 cases of uncomplicated seasonal hay-fever and has found only 47.9 per cent of patients sensitive to pollen alone.

For the purpose of this study, we have divided 100 patients with hay-fever, seen consecutively, into two clinical groups: the simple seasonal, 70 per cent, and the complex seasonal, 30 per cent. All the patients have been treated for at least two seasons. Those in the simple seasonal group present the typical history of fall hay-fever, the upper respiratory symptoms characteristic of the disease occurring only during the ragweed pollinating season. In the complex seasonal group we have listed only patients who have typical symptoms during the pollinating season of the ragweed but whose condition does not clear up completely after the first frost and who continue to have mild symptoms periodically throughout the year.

Sensitivities of Patients with Hay-Fever

Sensitive to	Seasonal Symptoms: 70 Cases	Perennial Symptoms: 30 Cases
Ragweed	70	30
Ragweed only	34	0
Other pollens	19	11
Dusts	12	20
Orris root	10	12
Epidermals	6	6
Foods	5	7
Cotton	0	2
Kapok	0	2
Flax	2	0
Silk	1	1
June fly	2	1

Here it must be emphasized that all of the 30 per cent in the complex group would be included in the simple group unless careful histories were obtained. In most patients, the extraseasonal symptoms were mild, varying from a few sneezes on arising to a tendency to colds and attacks of so-called bronchitis. In none were the symptoms of a severity comparable to those during the hay-fever season. These patients are not to be confused with those having perennial hay-fever with slight increase in symptoms during August and September.

All of these patients have been subjected to routine skin tests with thirteen pollens, the common epidermal proteins, orris root, cottonseed, kapok, flax, glue, silk, stock and autogenous house dusts, extracts of molds, June fly and foods. Attempts have been made in each instance to determine clinically the relation of the clue obtained by the positive skin test to the patient's symptoms. The accompanying table shows the sensitivities of these patients.

3. Vaughan, W. T.: Pollinosis: Constitutional and Local Factors, Arch. Int. Med. **40**:386 (Sept.) 1927.

4. Balyeat, Ray M.: Secondary Factors in Uncomplicated Cases of Seasonal Hay Fever, J. Lab. & Clin. Med. **14**:617 (April) 1929.

It will be noted at once that only thirty-four of the seventy simple cases, or 48.5 per cent, are pure ragweed cases and that in thirty-six, or 51.5 per cent, there are sensitivities to other substances of clinical importance even though the symptoms are present only during the pollinating season of the ragweed. In the complex group, not one patient was sensitive to ragweed alone. It is of further interest that the substances most commonly complicating the ragweed sensitivity are air borne. They will be discussed in the order of their frequency.

CAUSES OF HAY-FEVER

Other Pollens.—In northern Ohio, the pollens of lamb's quarters and of English plantain are the most common complicating factors. They are, however, the most simple to overcome, since the plants are not abundant and the pollen concentrations of the air are low. Ordinary precautions against pollen such as the avoidance of outdoor sports, automobile and train trips and sleeping in closed rooms or those ventilated with filters, solve most of the problems during the season when the pollens are first suspected of being complicating causes. Before the next season it is advisable to desensitize the patient to them as well as to the pollens of the ragweeds.

Dusts.—The next most common inhalant cause is in reality a group of substances. Samples of dust are obtained by means of muslin bags and a vacuum cleaner from beds, bedding, rugs, upholstered furniture and other sources of dust, each sample being obtained separately. The samples are extracted in Bernton's fluid, filtered and used for testing by the scratch method. The reacting substance is probably a mold or some other type of organism which contaminates the furniture from which the dusts are obtained. As evidence for this belief, we have the histories of a number of patients who were sensitive to extracts of the dusts from the mattresses on which they slept, but who did not react to cotton or cottonseed. The conditions cleared up when new cotton mattresses were substituted for the old ones, but all the patients had recurrence of symptoms after a few months. At this time the new mattress, previously harmless, contained a reacting material, and relief was obtained in each case by covering the mattress with rubber sheeting.

The allergen in these cases⁵ is not to be confused with house dust atopen as described by Coca,⁶ since he repeatedly stated that unconcentrated extracts as prepared by him never give positive reactions by the

5. Cohen, Milton B.: Asthma Due to Household Articles, *J. Lab. & Clin. Med.* **14**:837 (June) 1929.

6. Coca, A. F., and Milford, E. L.: Additional Notes on the Preparation of the Fluid Extracts and Solutions for Use in the Diagnosis and Treatment of Atopic Conditions, *J. Immunol.* **15**:1 (Jan.) 1928.

scratch method and that sensitivity to them can be determined only by intracutaneous testing. We are also fairly certain that the allergen is not identical with that of any of the common household materials such as wool, feathers, animal danders, orris root, etc. Its exact nature is unknown at present and further work is being done in an attempt to identify it.

Patients with sensitivity for dust complicating ragweed hay-fever have the sources of the allergen in their environment determined. If covering a mattress and pillow with rubber sheeting eliminates the contact, then that is all that is required. If, however, the living room furniture contains the substances or the patient must sleep in different beds because of the nature of his occupation, desensitization must be resorted to. This is usually successful. It is our custom to bring these patients to a relatively high level of tolerance by rapidly increasing the doses of the material injected, at any time of the year, and then to maintain the level by monthly or twice monthly injections. The main object is to have the tolerance high during the ragweed season.

The following cases illustrate these points very well.

CASE 1.—Mrs. B. C., aged 28, complained of hay-fever of the fall type complicated by asthma at the peak of the season for the past three years. There were no nasal or respiratory symptoms except in the period between August 15 and October 1. During the first season, she received coseasonal treatment with ragweed pollen without relief. During the second season, she used a Pollenair filter, but in spite of the pollen-free room for sleeping purposes, she still had symptoms. This result led us to search for a complicating cause, which was found in the dust from the mattress on which she slept. The mattress was covered with rubber sheeting. The attacks have been controlled ever since, and in 1929 a 100 per cent result was obtained from preseasonal desensitization.

CASE 2.—B. F., aged 50, was first seen in September, 1925, during an acute attack of hay-fever and asthma. Skin tests at that time were strongly positive to the pollens of grasses and ragweed and to orris root. The patient was placed in the hospital in a pollen-free room for one week, during which time the symptoms cleared up. In 1926, preseasonal desensitization with ragweed pollen extract was attempted. A dose of 0.5 cc. of 1:100 dilution was reached on August 12, but symptoms began on August 20 and were fairly severe. Orris root was removed from her environment and a pollen filter was installed in her bedroom. Still the symptoms did not disappear completely, although they were mild. In 1927, there was a repetition of the preseasonal treatment and of partial residence in filtered air, again without complete relief. It was at this time that she was tested to dusts obtained from her own mattress. A large reaction was obtained. The mattress was covered with rubber sheeting, and all symptoms disappeared promptly. After Sept. 1, 1927, there was complete relief. In 1928, complete relief was obtained again, this time by preseasonal treatment with ragweed pollen and the avoidance of contact with orris root and mattress dust.

Orris Root.—Orris root is one of the most common substances with which the mucous membrane of the average person comes in contact. It is used rather extensively in the manufacture of face powders, face

packs, astringent packs, cleansing creams, bath powders and bath salts. In addition, the oil is used in many perfumes and scented soaps. Since the women of the United States spend about \$250,000,000 yearly for cosmetics, contact with orris root can scarcely be avoided. It is therefore necessary to desensitize the average patient. As in the case of patients sensitive to dust, the desensitizing injections are begun at any time of the year and are carried rapidly to a peak, which is maintained by monthly injections of the largest dose reached. The treatment with ragweed is carried out in addition in the usual manner, as can be seen from the record of case 642, given here as case 3.

CASE 3.—Miss G. C., aged 35, was first seen in 1927. She had had fall hay-fever for the past three years. During the winter of 1927-1928, there had been a tendency to colds with occasional morning sneezing and slight itching of the roof of the mouth. These symptoms were not troublesome and information concerning them was elicited only by careful questioning. She considered herself to be perfectly well during the winter. Skin testing revealed the following positive reactions: short and giant ragweed, 10 plus; timothy and other grasses, 1 plus; orris root, 4 plus; pyrethrum, 2 plus; kapok, 2 plus; cottonseed, 1 plus; several foods, 1 plus.

Treatment was begun on June 19, 1928, with ragweed pollen extract, a dose of 0.15 cc. of 1:20 dilution being reached on August 20. In spite of this relatively large dose which was tolerated without any systemic reaction, symptoms began during the last week in August, when there was an average ragweed concentration of 180 pollen per cubic yard of air. The end-result was estimated at about 60 per cent relief, obviously not a result of which to be proud. An injection of 0.1 cc. of 1:100 dilution of ragweed extract was given once a month throughout the winter, and orris root desensitization was begun on Sept. 25. On December 1, a dose of 0.1 cc. of 1:100 orris root was reached. This and the same dose of ragweed were continued once monthly until June 11, 1929, when the doses of ragweed were increased at weekly intervals until 0.5 cc. of 1:20 ragweed was reached. The positive foods were removed from the diet and the mattress was covered with rubber sheeting. During the 1929 season, there was complete relief.

CASE 4.—Miss E. M., aged 18, was first seen on July 30, 1928. She had had fall hay-fever for seven years without winter symptoms, except for a slight tendency to "colds." In 1926 and again in 1927, she had preseasonal treatment with ragweed pollen by a capable allergist with only partial relief. Skin tests revealed reactions to the following substances: grass pollens, 3 plus; short and giant ragweed, 1 plus; orris root, 2 plus; stock mattress dust, 3 plus; patient's mattress dust, 10 plus; bedroom rug dust, 3 plus; dining room rug dust, 1 plus; couch in living room dust, 10 plus; sun room chairs dust, 4 plus.

Ragweed desensitization was begun immediately, and a dose of 0.15 cc. of 1:20 dilution was reached on August 18. Attempts were made to avoid orris root, the bedroom was freed from the offending dusts, and the other furniture containing the reacting dust was avoided by the patient. The result was estimated at 70 per cent, as there were symptoms during the week of the peak of the ragweed pollination. On October 13, orris root desensitization was begun, and on November 17 dust desensitization was started in addition. High concentrations of each were reached by June, 1929, when the treatment with ragweed was

recommended. On August 18, a dose of 0.1 cc. of 1:20 extract was reached. In 1929, the result was 100 per cent satisfactory; there were no symptoms. In addition, the patient had no "colds" during the preceding winter.

Epidermal Proteins.—In our experience, feather proteins are not as important in the etiology of hay-fever and of asthma as has been noted by others. We find, for example, that when our feather extracts are made from new feathers, reactions are small and few. When, however, we obtain used feathers from feather renovating plants, our extracts give large and frequent reactions. The latter reactions are due to some contaminant in the feathers, which so far as we have been able to determine, seems to be identical with the reacting substance called by us mattress dust. We therefore use feather extracts made from new feathers and believe that this accounts for the differences between our results and those published by other observers. Rabbit hair is a much more common offender than the other animal hairs because it is used more extensively, although all animal hairs may be allergens.

When patients with hay-fever give reactions to any epidermal proteins, an attempt is made to free the patient's environment from the suspected material. This usually suffices, but if avoidance is difficult, desensitization must be attempted.

Foods.—Almost any food may be a complicating factor in seasonal hay-fever. It is a safe procedure to eliminate any foods giving positive skin tests or suspected from the history to be a cause of symptoms from the diet during the pollinating season of the ragweed.

Miscellaneous.—Several other substances are occasionally of clinical importance, as may be seen from the accompanying table. Cotton, kapok, flax and silk are present in everyone's environment, and patients having clinical symptoms caused by them must be desensitized.

June fly as a cause of hay-fever is a distinct factor in the region of Lake Erie. A complete report on this subject has been made by Figley.⁷

SUMMARY AND CONCLUSIONS

A review of the histories of 100 patients with ragweed hay-fever, seen consecutively, reveals that 30 per cent have very slight symptoms at other times of the year which are generally overlooked by the patient and the physician. All of these patients gave reactions to some substance other than ragweed pollen. Among the 70 per cent with seasonal symptoms, only thirty-six were sensitive to some substance other than ragweed pollen, so that only 34 per cent of so-called ragweed hay-fever is uncomplicated by other sensitivities. It is significant that the percentage of complete relief following preseasonal treatment is around

7. Figley, Karl D.: Asthma Due to the May Fly, *Am. J. M. Sc.* **178**:338 (Sept.) 1929.

40, and a check of our records shows that the large majority of complete seasonal cures in our cases were obtained in patients sensitive to ragweed alone. Discovery of the complicating sensitivities, the elimination of contact with them or desensitization to them results in complete seasonal cure in the majority and marked benefit in all other cases. There are no complete failures as in previous years. Experience demonstrates that the care of allergic patients is a complex problem requiring cooperation between physician and patient in intensively studying each case as an individual problem. It is desirable to have patients with hay-fever under treatment during the entire year, so that complicating factors may be discovered and eliminated before ragweed desensitization is begun.

10616 Euclid Avenue.

LIPOID NEPHROSIS OF UNUSUAL DURATION

II. PATHOLOGIC-ANATOMIC REPORT *

WILHELM EHRLICH, M.D.

NEW YORK

It is my object to present in this paper the pathologic-anatomic changes in a case of lipoid nephrosis which furnishes a valuable contribution not only to the question of the terminal stage of this disease but also to other questions. When speaking of lipoid "nephrosis," I am fully conscious of the inadequacy of this term. Aschoff¹ was right to deduce that this term is incorrect and should be replaced by lipoid "nephrodystrophia" or "nephropathia." If here, nevertheless, the term "nephrosis" is used, it is done not only because it is generally accepted by the clinicians, but especially because it is not proved whether this disease is of a purely degenerative nature, as is supposed by Volhard and Fahr² and Munk,³ or whether it is an inflammation to begin with, as is believed by Aschoff,⁴ Schlayer⁵ and Bohnenkamp.⁶ Aschoff supported his opinion mainly by the fact that in all slides of genuine nephrosis presented to him by Volhard, he found changes in the glomeruli which indicated older inflammatory processes. Furthermore, he ascribed to the epithelial cells defensive properties which he believed to be the essence of inflammation. Bohnenkamp, who followed similar ideas, relied mainly on the Uranium experiments of Suzuki.⁷

* Submitted for publication, Nov. 14, 1929.

* From the Hospital of The Rockefeller Institute for Medical Research.

1. Aschoff, L.: *Kritisches zur Lehre von der Nephritis und der Nephropathien*, Med. Klin. **9**:18, 1913; *Ueber den Begriff der "Nephrosen" und "Sklerosen"*, Deutsche med. Wchnschr. **43**:1345, 1917.

2. Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit*, Berlin, 1914. Volhard, F.: *Die doppelseitigen haematogenen Nierenerkrankungen*, Berlin, 1918; *Ueber Wesen und Behandlung der Brightschen Nierenkrankheiten*, Deutsche med. Wchnschr. **44**:393, 1918. Fahr, T.: *Zur Frage der Nephrosen*, Berl. klin. Wchnschr. **55**:993, 1918; *Ueber Nephrosen*, Deutsches Arch. f. klin. Med. **125**:66, 1918; *Beiträge zur Frage der Nephrose*, Virchows Arch. f. path. Anat. **239**:32, 1922; *Pathologische Anatomie des Morbus brightii*, Handbuch d. spez. path. Anat. u. Hist. **6**:156, 1925.

3. Munk, F., *Klinische Diagnostik der degenerativen Nierenerkrankungen*, Ztschr. f. klin. Med. **78**:1, 1913; *Die Nephrosen*, Med. Klin. **12**:1019 and 1047, 1916; *Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren*, Berlin, 1918.

4. Aschoff, L.: *Lehrbuch der pathologischen Anatomie II*, Jena, 1921.

5. Schlayer: *Ueber die Nephrosen*, Med. Klin. **14**:53, 1918.

6. Bohnenkamp, H.: *Zur Frage der Nephrosen*, Virchows Arch. f. path. Anat. **236**:380, 1922.

7. Suzuki, T.: *Zur Morphologie der Nierensekretion*, Jena, 1912.

The number of cases reported in which the patients have come to autopsy is still small and may not exceed from twenty to thirty. In all, the duration was from a few months to three years. In my case the condition lasted for about seventeen years, and the patient was under continuous clinical control during the last six years. Before discussing the case, I shall report the observations. As the clinical part has been reported in detail by Johnston and MacKay,⁸ I shall call attention only to the important points of the clinical observations.

REPORT OF CASE

History.—M. M., a man, aged 19, had had attacks of edema of from two to three weeks' duration at least every year, and usually more often, since the sixteenth



Fig. 1.—Longitudinal section through the right kidney after Jores fixation.

month of life. In January, 1923, he had pneumonia, in July of the same year, appendicitis with "pus in the abdominal cavity," and in February, 1926, bronchopneumonia. During the last six years, there were recurring periods of edema and oliguria. The amount of albumin was 1.4 per cent. In the sediment casts, fatty epithelial cells, leukocytes and many doubly refractile lipid bodies, were observed. Rare erythrocytes were said to have been seen, but on only four of the many examinations made. No cardiac enlargement was noted, no retention of nitrogen and no increase in the blood pressure. There were no symptoms of syphilis. On Nov. 27, 1928, the patient developed symptoms of diffuse peritonitis and died on Dec. 2, 1928.

Autopsy.—Only a partial autopsy was permitted. This was performed about two hours after death. The body was that of a fairly well nourished man, showing no rigor mortis but a slight livor mortis. The body showed marked edema of the

8. Johnston, C., and MacKay, E. M.: Lipoid Nephrosis; Report of a Case of Unusual Duration, Arch. Int. Med., this issue, p. 734.

legs and face. The peritoneal cavity was opened through a small incision and was found filled with about 2 quarts of greenish, purulent fluid (*Streptococcus hemolyticus* peritonitis).

The kidneys were large and pale; each weighed about 300 Gm. The capsule stripped easily. The surface was pale yellowish and was smooth, with indications of fine, light violet depressions. Cross-section showed the cortex much enlarged, measuring from 9 to 20 mm. It was pale yellowish and contained fine, light violet striae radiating inward from the capsule (fig. 1). The cortex was fairly well marked off from the medulla. In the pelvis a few hemorrhages were seen.

Microscopic Examination.—The normally more uniform cortical structure had, in most places, been replaced by broad striations radiating inward from the capsule to the medulla (fig. 2). A narrow, light, subcapsular zone was joined by

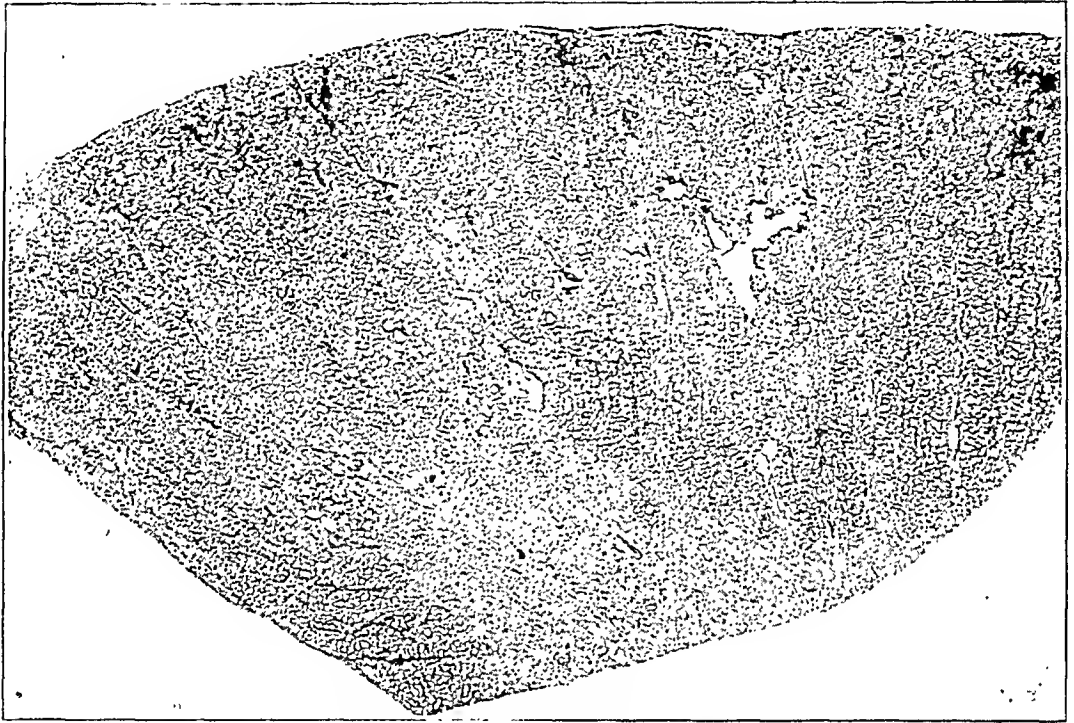


Fig. 2.—Low magnification showing the grossly striated structure of the cortex. Iron-hematoxylin-eosin; $\times 5$.

an irregular zone which was similar to the usual cortical structure. From here, broad, light colored areas, separated by narrow, dark striae, converged toward the medulla.

Under higher magnifications, the lighter parts were seen to correspond mainly to enlarged tubules, the character of which as major pieces⁹ was still distinct in many places (fig. 3). These tubules were lined partly by greatly swollen and vacuolated or fatty degenerated epithelial cells which in some instances entirely closed the tubules, and partly by epithelial cells which had undergone considerable hyaline droplet-like degeneration (fig. 4). For the most part, these vacuolated and hyaline droplet-like degenerated tubules lay alternating side by side. In other

9. The term "major pieces" refers to the convoluted tubules lined by large epithelial cells in contradistinction to the tubules lined by small epithelial cells, which are designated as minor parts.

places they had a more localized distribution. In some instances they passed over into each other. It should be mentioned that the hyaline droplet-like degenerated tubules were located in the half of the cortex next to the medulla. The epithelial cells, mainly of the hyaline droplet-like degenerated major pieces, frequently contained pyknotic nuclei or had lost them entirely. In many places the epithelial cells were desquamated. In such places one found signs of regeneration. Gaps in the epithelial layer were covered by epithelial cells which resembled endothelium (fig. 3) and contained karyokinetic figures here and there. In the basal parts of the epithelial cells one saw nearly everywhere fine fat globules,

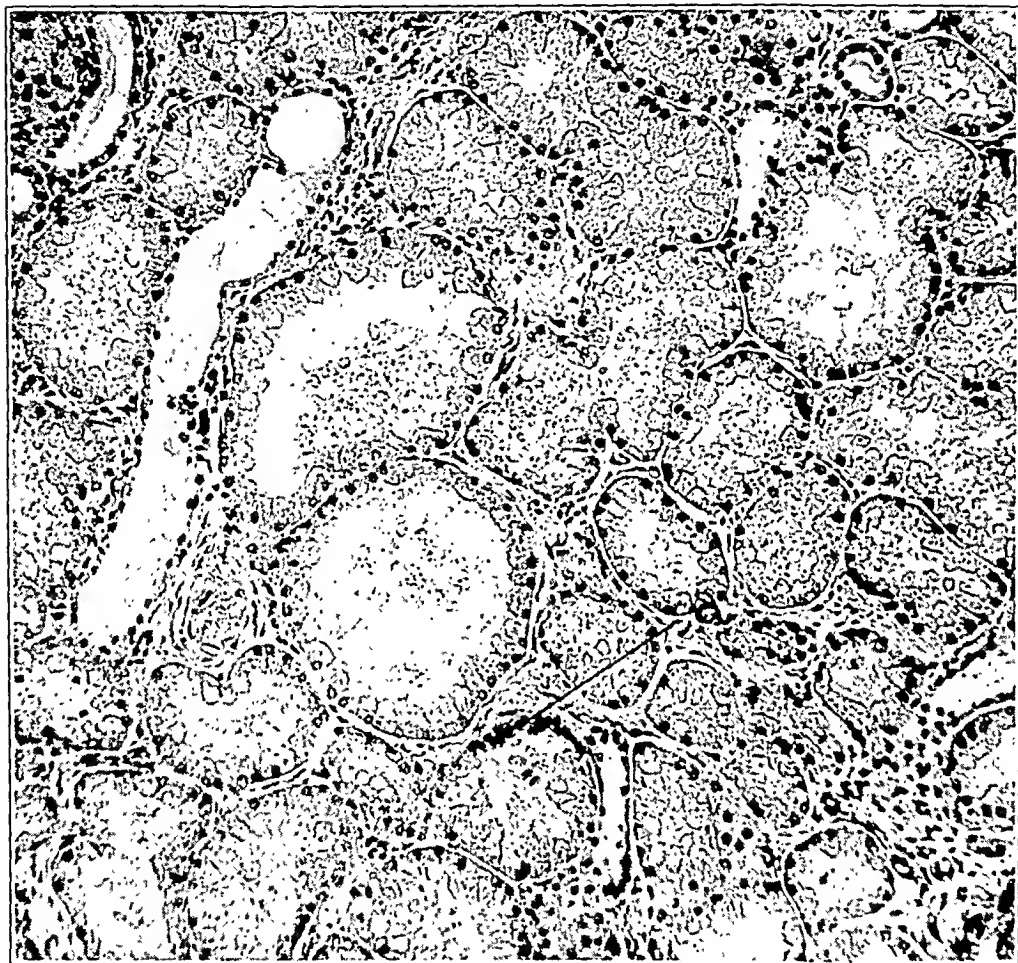


Fig. 3.—Partly hyaline droplet-like, partly fatty or vacuolated degenerated major pieces (convoluted tubules). In the lumina of the tubules is mainly coagulated protein. Regeneration in a gap of the epithelial layer (*a*). The interstitial tissue is well preserved. Iron-hematoxylin-eosin; $\times 160$.

most of which were doubly refractile. Within the lumina of the tubules one found coagulated protein, some desquamated epithelial cells, and in some places also polymorphonuclear leukocytes. In the hyaline droplet-like degenerated major pieces one saw also hyaline drops within the lumina. The minor parts of the light parts of the cortex contained fairly large numbers of casts, which increased in number toward the medulla. The interstitial tissue of these parts of the cortex appeared to be normal in most places (fig. 3).

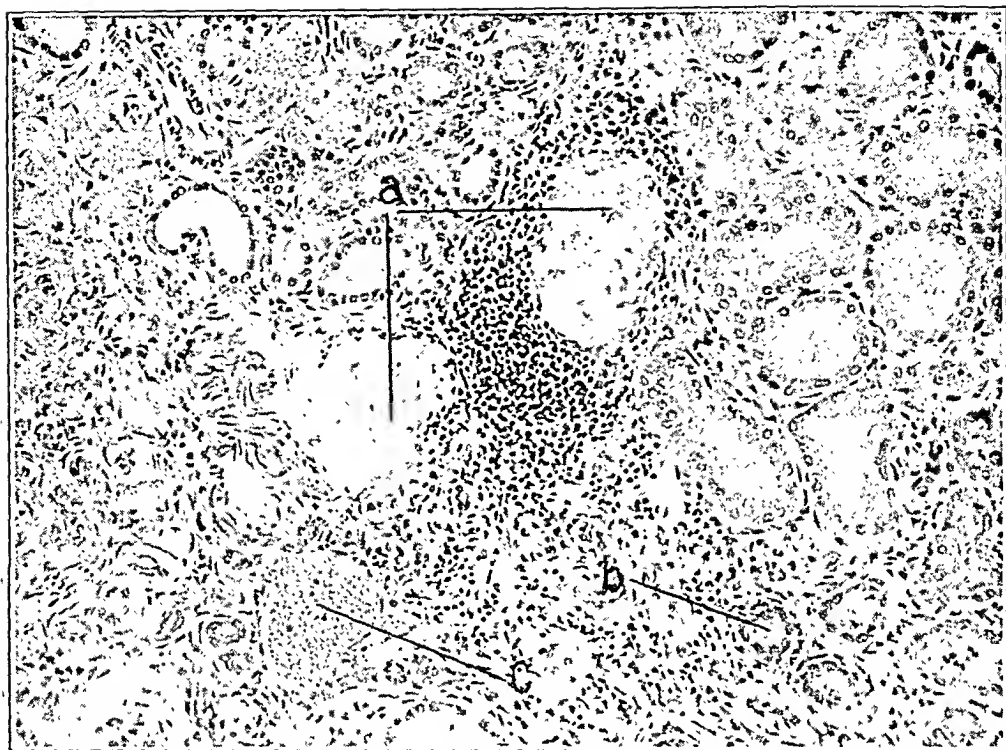


Fig. 5.—Scar with two completely hyalinized glomeruli (*a*). Between them is an infiltration of small, round cells. Degenerated tubule with a few surrounding polymorphonuclear leukocytes (*b*) is seen and (*c*) a small vein dilated with blood. Iron-hematoxylin-eosin; $\times 160$.

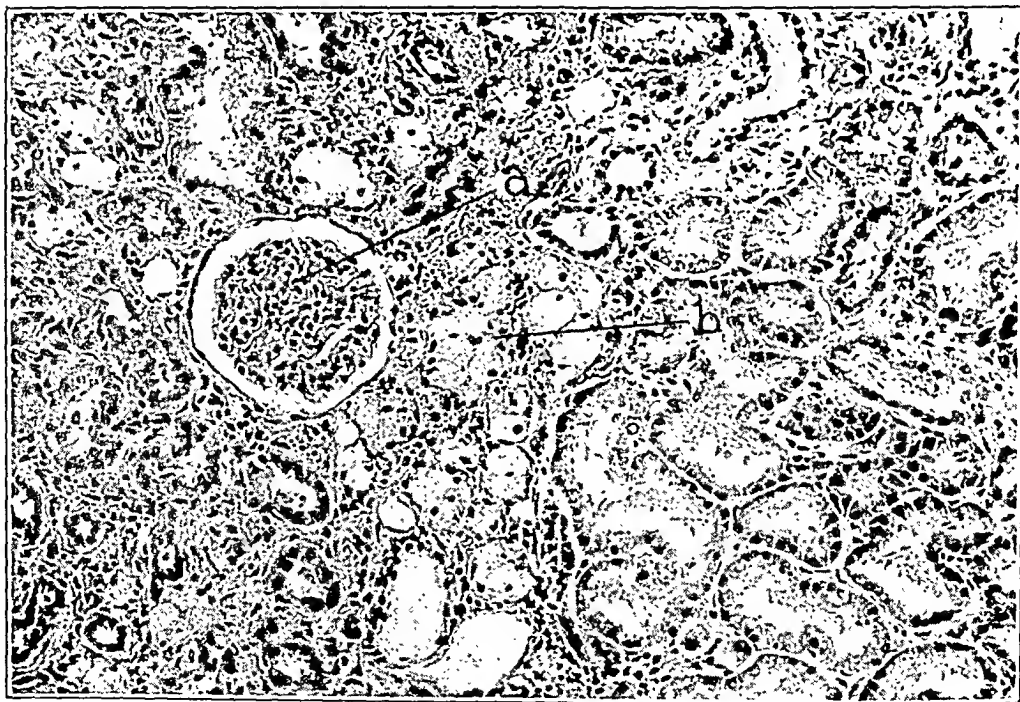


Fig. 6.—Intact glomerulus well filled with blood (*a*). In the interstitial tissue many xanthoma-like fat cells (*b*) are shown. Iron-hematoxylin-eosin; $\times 160$.

of normal size and some enlarged. The enlarged glomeruli contained, according to the method of Mertz,¹⁰ increased numbers of nuclei, but the increase corresponded to the increase in the size of the glomeruli. In a few places one also found small accumulations of endothelial cells in a single loop (fig. 7). The loops of the well preserved glomeruli were delicate and mostly well filled with blood. Occasionally, the glomerular spaces were dilated and contained coagulated protein. There was only little fat to be found in the covering cells of the glomeruli. In these glomeruli, inflation or adhesions of the loops, increased numbers of polymorphonuclear leukocytes or protoplasmic masses within the loops were nowhere to be found. There were no erythrocytes and no fibrin in any of the glomerular spaces. No hernia-like descension of loops into the tubules was seen, nor were there adhesions of the glomeruli to the capsules. Neither were the epithelial cells of these glomeruli changed, except for the slight fatty degeneration already mentioned.



Fig. 7.—Enlarged glomerulus with a small accumulation of endothelial cells in a single loop (a). Elastica-van Gieson stain; $\times 160$.

The other 50 per cent of the glomeruli were in all stages of hyaline degeneration. They were localized in the scarred parts of the cortex, partly single and partly in small groups. One saw well preserved glomeruli, the capsules of which were concentrically thickened by a substance which stained red by van Gieson (fig. 8). Other glomeruli contained hyalinized loops, especially at the place of entry of the vessels (fig. 9). These glomeruli were occasionally adherent to the capsule. A few of these glomeruli showed a slight proliferation of the parietal capsular epithelium (fig. 9), but there were no crescent formations. About a third of the glomeruli were entirely hyalinized (fig. 5) and were sharply demarcated from the surrounding tissues.

10. Mertz, A.: Ueber die quantitativen Zellverhältnisse der Glomeruli bei Glomerulonephritis, *Centralbl. f. allg. Pathol. u. path. Anat.* **29**:321 (1918).



Fig. 8.—Concentric thickening of a glomerular capsule, poor in nuclei, with beginning hyalinization of the glomerulus at the place of entry of the artery. In the surrounding interstitial tissue there is an increased number of collagenous fibers (appearing dark in the photomicrograph). Elastica-van Gieson stain; $\times 160$.

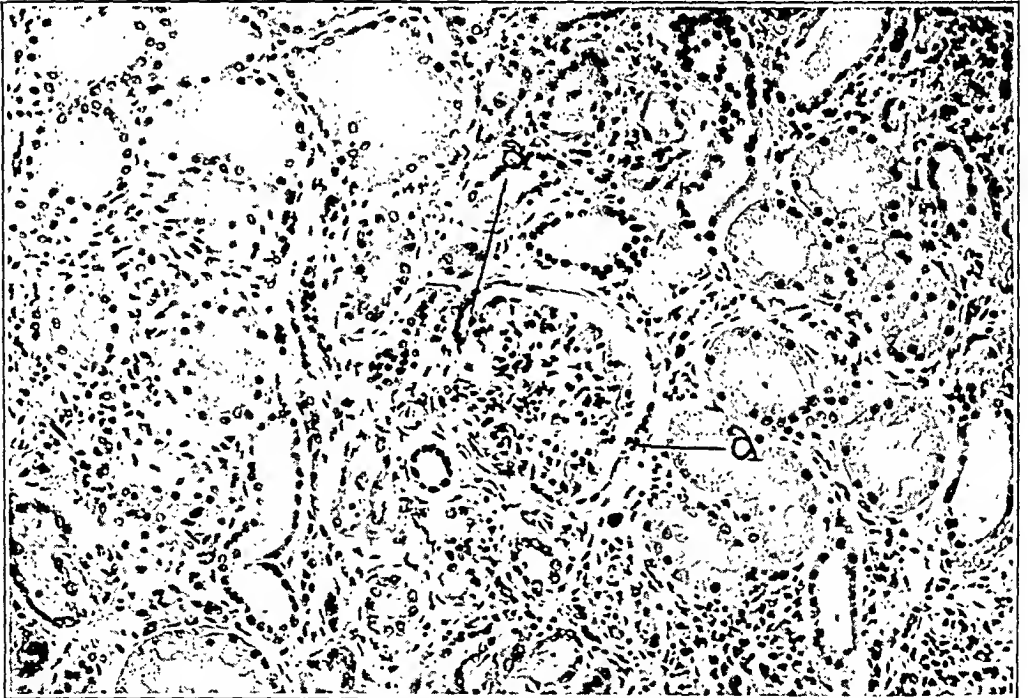


Fig. 9.—Advanced hyalinization of a glomerulus with a slight proliferation of the parietal epithelial cells (a). Iron-hematoxylin-eosin; $\times 160$.

The medulla was rich in collagenous connective tissue, which was swollen in places and contained some polymorphonuclear leukocytes and round cells. In the tubules of the medulla many casts were seen and in one place also a few erythrocytes. The arterioles were well preserved. The larger arteries showed a moderate degree of intimal hyperplasia.

All amyloid reactions made were negative.

COMMENT

In a discussion of this case one has to consider first whether or not one is dealing with a genuine lipoid nephrosis. Under the differential diagnostic point of view, there has to be considered only the subchronic glomerulonephritis of Volhard,¹¹ with nephrotic tendency, i. e., the intracapillary form of Fahr.¹² Munk¹³ especially called attention to the difficulties which frequently arise in differentiating late stages of "subacute glomerulonephritis" from nephrosis, anatomically. Both of them show the picture of large white kidney. Volhard,¹⁴ however, mentioned that in a subchronic glomerulonephritis one usually sees macroscopic hemorrhagic dots on the renal surface. Fahr¹⁵ even stated that small hemorrhages are invariably present. Such dots were entirely absent in the case herein reported.

Microscopically, in subchronic glomerulonephritis, the glomerular lesions are outstanding. One finds enlargement and anemia of the glomeruli, enormous increase in number of the endothelial elements, adhesions of the loops and erythrocytes in the glomerular spaces. In this case, none of these changes were found. Most of the well preserved glomeruli seemed to be entirely normal. It is true that a few glomeruli showed increased numbers of nuclei and that, in single hyalinized glomeruli, slight proliferations of the parietal epithelial cells were seen, but these observations are in entire accord with the observations of Fahr¹⁶ and others, who stated that one finds them more frequently in later stages of lipoid nephrosis. The increase in the number of nuclei is, as Fahr believed, of a secondary inflammatory nature. If one takes into consideration that in this case the increase was not out of proportion to the size of the glomeruli, and that no other inflammatory lesions were found, it is reasonable to assume that here the increase of nuclei was merely an expression of compensatory hyperplasia of these glomeruli. Unfortunately, little is known about the histology of compensatory hypertrophy and hyperplasia of the glomeruli, and it

11. Volhard (footnote 2, first, second and third references).

12. Fahr (footnote 2, first and seventh references).

13. Munk (footnote 3, third reference).

14. Volhard (footnote 2, second and third references).

15. Fahr (footnote 2, seventh reference).

16. Fahr (footnote 2, fourth, fifth and sixth reference).

seems to be necessary to study this question thoroughly before it can be discussed further. Concerning the proliferation of the parietal epithelial cells, which was observed in single hyalinized glomeruli, one may join Volhard,¹⁴ who considered it a plain reaction of the epithelial cells to the hyalinization.

Furthermore, if the clinical observations are taken into consideration—I mention again only the absence of increase in blood pressure which is emphasized so much by Volhard¹⁴—there can be no more doubt that in this case there was a genuine lipoid nephrosis. The occasional reports of the presence of erythrocytes in the urine cannot change the diagnosis, mainly because they are said to have been seen on only four of the many examinations made, and the accuracy of some of these examinations has already been questioned.⁸ Slight hemorrhages have been seen also by Volhard and Fahr¹⁷ and other observers. Fahr¹⁸ occasionally found them within the tubules. According to him, they are small hemorrhages from overcrowded capillaries caused by passive congestion. In the case herein reported, likewise, some erythrocytes were found, but in one tubule only, and there were also hemorrhages in the pelvis of the kidneys which may account for the occasional presence of erythrocytes in the urine.

It is well known that the question whether or not there is a genuine nephrotic contracted kidney is much disputed. Whereas Munk¹⁹ and Fahr¹⁵ stated the belief that the lipoid nephrosis leads to contracted kidneys, Aschoff,⁴ Volhard¹⁴ and Herxheimer²⁰ expressed great doubts concerning this theory. The two cases presented in the monograph of Volhard and Fahr¹⁷ and also the case of Mason²¹ cannot stand severe criticism. In spite of a duration of seventeen years, the patient in the case herein reported still had much enlarged kidneys. Although as a rule one case is of no great importance, one may be entitled to draw conclusions in this case, especially because it seems to be the only genuine case of lipoid nephrosis of long duration ever observed. It seems to be certain that lipoid nephrosis can last indefinitely, in some cases at least, without leading to contracted kidneys.

The cause of death in the case reported was peritonitis, so common in lipoid nephrosis. The organism, however, was not a pneumococcus, as is usually the case, but *Streptococcus hemolyticus*.

17. Volhard and Fahr (footnote 2, first reference).

18. Fahr (footnote 2, fourth and fifth references).

19. Munk (footnote 3, second and third references).

20. Herxheimer: Ueber den jetzigen Stand unserer anatomischen Kenntnisse der Nephritis und Nephropathien, Munchen. med. Wchnschr. **65**:283, 1918.

21. Mason, E. H.: The Life History of a Case of Nephrosis, Internat. Clin. **1**:163, 1926.

SUMMARY

A case of genuine lipoid nephrosis has been reported in which the conditions lasted for about seventeen years and showed clinically as well as anatomically all the signs of this disease.

Several questions concerning lipoid nephrosis have been discussed. As at autopsy the kidneys were still much enlarged, it seems to be doubtful whether true lipoid nephrosis leads to contracted kidneys.

CHEMICAL DETERMINATION OF THE GLYCOGEN RATIO IN THE BUNDLE OF HIS AND THE CARDIAC MUSCLE IN MAN AND IN THE HORSE *

WALLACE M. YATER, M.D.

WASHINGTON, D. C.

AND

ARNOLD E. OSTERBERG, PH.D.

AND

HANS W. HEFKE, M.D.

Fellow in Radiology, the Mayo Foundation

ROCHESTER, MINN.

For years the question of the amount of glycogen in the bundle of His, as compared with the amount in the cardiac muscle, has been discussed. The general impression, until recently at least, has been that the conduction system is comparatively rich in glycogen. This conclusion has been reached as the result of studies of microscopic sections with stains, especially Best's carmine stain. When the work on which this idea was based is analyzed, however, one feels that with the inaccurate staining methods employed the question has hardly been settled.

REVIEW OF SIGNIFICANT LITERATURE

Best,¹ in 1903, published the results of a study on glycogen and described a method of staining which he considered to be fairly specific for glycogen. He found that a carmine stain of unknown chemical composition was taken up by certain granules present in the fixed tissues of the liver, of striped muscle, of tumors and of inflammatory lesions. These could be demonstrated also with iodine and were dissolved by saliva and weak acids. He concluded that these granules contained glycogen, which was more or less loosely combined with proteins in a manner similar to the glycosides. Since then, other stains have been suggested for demonstrating glycogen in the tissues, but Best's carmine has been considered the most reliable.

Mönckeberg,² in 1908, using staining methods, concluded that the fibers of cardiac muscle of human beings are always glycogen-free in

* Submitted for publication, Oct. 23, 1929.

1. Best: Ueber Glykogen, insbesondere seine Bedeutung bei Entzündung und Eiterung, Beitr. z. path. Anat. u. z. allg. Path. **33**:585, 1903.

2. Mönckeberg, J. G.: Untersuchungen über das Atrioventrikularbündel im menschlichen Herzen, Jena, 1908.

postuterine life, and that the amount of glycogen in the Purkinje fibers is variable, depending on the state of nutrition. There was no glycogen in these fibers when a patient was in a state of marked cachexia.

Aschoff and Nagayo,³ in 1908, having conceived the idea that possibly the vacuolated appearance and clearness of the Purkinje fibers might be due to glycogen, determined by the staining method that the Purkinje fibers of the heart of the sheep, beef and calf contained much more glycogen than the muscle fibers. This applied to the entire conduction system distal to the auriculoventricular node. In the pig's heart, the reverse was true; the glycogen content of the Purkinje fibers was small. In thirty hearts of human beings fixed from five to twenty-four hours after death, the results were variable, but in eighteen, glycogen was not found in the fibers of the specific system; in nine a very small amount was found, and in only three a very large amount. It was the belief of these investigators that the Purkinje fibers do not contract with the cardiac muscle (shown later by Pick⁴ to do so) and that, therefore, they do not need as much glycogen, and store it. In considering this work, Marchand⁵ claimed that he was the first to point to the glycogen content of the Purkinje fibers in the heart of the horse, and that this large amount indicated the embryonal nature of these fibers.

Arnold,⁶ in 1909, suggested that the relatively large amount of glycogen in the bundle of His might be used to demonstrate it in sections.

Engel,⁷ in 1910, examined the heart of a woman, aged 64, who had been cachectic. The auriculoventricular bundle contained abundant glycogen, but the cardiac muscle did not contain any.

Berblinger,⁸ in 1912, examined eighteen hearts of human beings fixed from one to five hours after death and stained with Best's carmine. In five of them he found the glycogen to be of equal amount in the specific system and in the cardiac muscle; in five the amount was about

3. Aschoff and Nagayo: Ueber den Glykogengehalt des Reizleitungssystems des Säugetierherzens, *Verhandl. d. deutsch. path. Gesellsch.* **12**:150, 1908.

4. Pick, E. P.: Ueber das primum und ultimum Moriens im Herzen, *Klin. Wchnschr.* **3**:662-667, 1924.

5. Marchand, F.: Ueber eine Geschwulst aus quergestreiften Muskelfasern mit ungewöhnlichen Gehalte an Glykogen, nebst Bemerkungen über das Glykogen in einigen fötalen Geweben, *Virchows Arch. f. path. Anat. u. Physiol.* **100**:42, 1885.

6. Arnold, Julius: Zur Morphologie des Glykogen des Herzmuskels nebst Bemerkungen über dessen Struktur, *Arch. f. Entwcklungsmechn. d. Organ.* **73**:726, 1909.

7. Engel, Irmgard: Beiträge zur normalen und pathologischen Histologie des Atrioventrikulärbündels, *Beitr. z. path. Anat. u. z. allg. Path.* **48**:499, 1910.

8. Berblinger, Walther: Das Glykogen im menschlichen Herzen, *Beitr. z. path. Anat. u. z. allg. Path.* **53**:155, 1912.

the same in both, in five it was present only in the fibers of the bundle. in one it was present only in the auricular muscle, and in two it was absent throughout. He maintained that in the healthy heart the muscle fibers frequently contained considerable glycogen, and that the auricular muscle contained much glycogen even when the remainder of the heart was found to be free of it. He did not believe that glycogen was necessarily absent in states of cachexia.

In studying the relationship of the amount of glycogen to the amount of fat in hearts of rabbits, Lipska-Mlodowska,⁹ in 1918, found less glycogen demonstrable with stains than by the use of the chemical method. From this she concluded that estimation of the amount of glycogen, microscopically, is difficult and subjective. She contended, also, that the muscle fibers of the heart and the fibers of the bundle of His may store both fat and glycogen.

Eisner,¹⁰ in 1926, compared the staining method with Pflüger's chemical method, as a means of estimating the amount of glycogen, and found that the results corresponded fairly well.

Arndt,¹¹ in 1928, determined that the glycogen in the cardiac muscle is not diminished in cases of starvation in animals as it is in the liver and the voluntary muscles.

Buadze and Wertheimer,¹² in 1928, apparently were the first to make quantitative chemical determinations of the glycogen in the conduction system as compared with that in the cardiac muscle. They had noticed that Best's carmine stain often gave results which were contrary to the results of chemical estimation. They felt that the specific system, the main function of which is conduction, should not require as much glycogen as the contracting muscles. These investigators dissected out the main left bundle branches of the hearts of horses where they were subendocardial, near the apex, and determined the glycogen content by Pflüger's method as compared with the glycogen content of muscle from the interventricular septum. In all cases the cardiac muscle contained

9. Lipska-Mlodowska, Stephanie: Zur Kenntnis des Muskelglykogen und seiner Beziehungen zum Fettgehalt der Muskulatur, *Beitr. z. path. Anat. u. z. allg. Path.* **64**:18, 1918.

10. Eisner, Georg: Ernährungsschädigungen in ihrer Bedeutung für Blutzucker und Glykogengehalt der Organe, *Ztschr. f. d. ges. exper. Med.* **52**:214, 1926.

11. Arndt, Hans-Joachim: Vergleichend-morphologische und experimentelle Untersuchungen über den Kohlydrat- und Fettstoffwechsel der Gewebe, *Vorbemerkung über die Anlage der Arbeit*, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:69, 1927; *Vergleichend-morphologische und experimentelle Untersuchungen über den Kohlydrat- und Fettstoffwechsel der Gewebe*, *Vorbemerkung zur experimentellen Methodik*, *ibid.* p. 523.

12. Buadze, S., and Wertheimer, E.: Der Glykogengehalt des Reizleitungssystems im Herzens, *Pflüger's Arch. f. d. ges. Physiol.* **219**:233, 1928.

much more glycogen than the specific system; the average ratio was 7:1. This was true whether the tissues were examined half an hour or fourteen hours after death. They also tested the oxygen consumption of the specific system as compared with that of the cardiac muscle in three hearts, and found that the oxygen consumption of the latter was much greater. A natural conclusion from these studies was that the staining methods for determining the amount of glycogen in tissues is unreliable.

The results of Buadze and Wertheimer were so surprising, in view of the conclusions of other investigators, that we were stimulated to verify the work.

METHOD OF STUDY

It was thought desirable to determine by chemical methods the amount of glycogen present in the bundle of His and in the cardiac muscle in man. Such data had never before been obtained. Two procedures were necessary: The bundle of His had to be dissected out carefully but quickly from relatively fresh hearts, and a chemical method had to be developed that would give accurate results with a few milligrams of tissue. By repeated efforts it became possible to dissect cleanly, from its so-called sheath, the main portion of the auriculoventricular bundle in a large percentage of hearts of adult subjects within a few minutes. In some cases a large part of the right main bundle branch also could be isolated. These tissues weighed only a few milligrams. All of these specimens were examined microscopically in order to ascertain that the bundle had actually been isolated. Every bundle that we examined chemically had been cleanly removed.

Dissection.—In the dissection, the central fibrous body and the membranous portion of the interventricular septum were opened carefully by a sharp-eye knife just above the attachment of the septal cusp of the tricuspid valve and just at the line of juncture of the membranous portion with the muscular portion of the interventricular septum. Figure 1 illustrates a cross-section of the bundle of His and gives an idea of the thinness of the so-called sheath that surrounds the bundle, as well as the relation of the bundle to the interventricular septum. Once the point of the knife has entered this sheath it may be slit open, thus exposing the bundle. The bundle may then be dissected out with a blunt-pointed instrument, backward to the auriculoventricular node and forward to the point of division into the right and left bundle branches. Occasionally the right bundle branch, which is very small, may be dissected out as it runs downward in the interventricular septum to the base of the right anterior papillary muscle (fig. 2). The left bundle branch may also be exposed at times, but it is so flat and broad that it rarely can be removed. The bundle of His and its right branch grossly resemble nerves; they appear almost white and almost round on cross section. After we had examined a series of hearts of human beings, we studied hearts of horses by a somewhat similar method. In the latter, it was found necessary to adopt the method of dissection used by Buadze and Wertheimer and originally described by Peterson¹³ and by Schauder.¹⁴ It is almost impossible to isolate

13. Peterson, G.: Ueber das atrioventrikuläre Reizleitungssystem bei den Haussäugetieren, *Arch. f. wiss. und prakt. Tierheilkunde* 44:97, 1918.

14. Schauder, W.: Makroskopische Darstellung des Atrioventrikulären Verbindungsbündels im Herzen des Pferdes, *Arch. f. wiss. und prakt. Tierheilkunde* 44:373, 1918.



Fig. 1.—*a.v.b.*, cross-section of the bundle of His of the heart of the human being showing the thinness of the sheath surrounding it; *m.s.*, membranous portion of interventricular septum; *i.v.s.*, muscular portion of interventricular septum ($\times 20$).



Fig. 2.—Right auricle and ventricle of the heart of a human being opened to expose the interventricular septum. The bundle of His and the right bundle branch have been exposed by dissection. *A*, the bundle of His; *B*, the right bundle branch.

the bundle of His in the heart of a horse as we did in the heart of human beings, because it is buried in the subaortic musculature. One must begin the dissection in two constant false chordae tendineae in the left ventricle which converge on the interventricular septum about midway between the apex and the aortic valves. After uniting, the Purkinje fibers of the two chordae flatten out subendocardially, ascend as a thin, flat, whitish bundle for a short distance, and then pass obliquely into the subaortic musculature as the main left bundle branch. We used these portions of the conduction system in the heart of the horse. The identity of the left bundle branch in the hearts of the horses was verified in each case by the microscopic sections stained with van Gieson's preparation. There was always much more fibrous tissue in these specimens than in the bundle of His in the

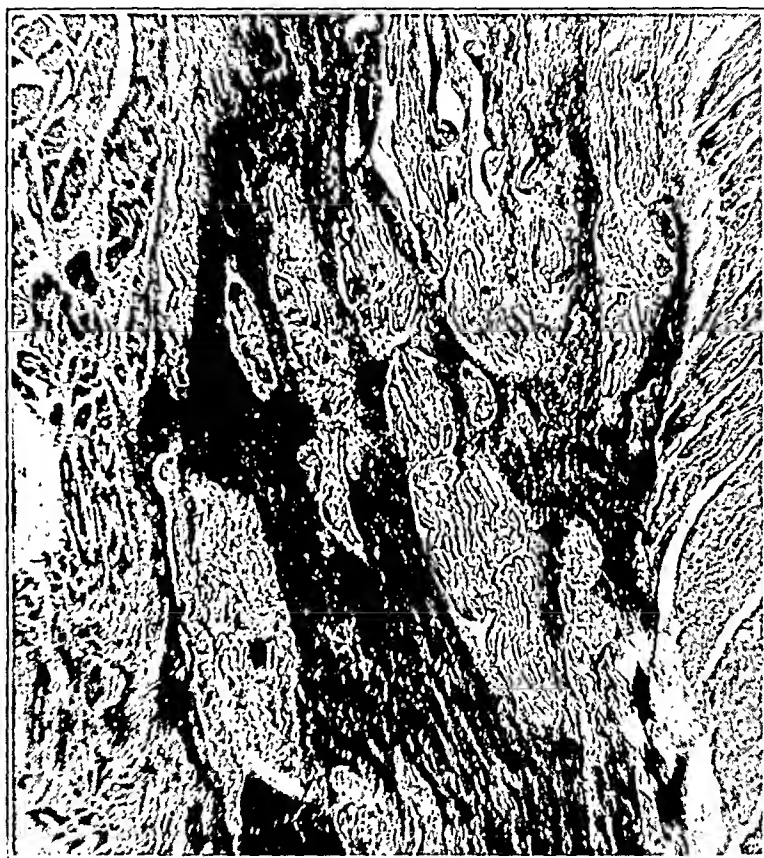


Fig. 3.—Longitudinal section of left bundle branch of the heart of a horse, showing large amount of fibrous tissue. Cardiac muscle is seen on each side of the bundle ($\times 40$).

human being, which was evident macroscopically also. Perhaps from 20 to 50 per cent of the left bundle branch of the heart of the horse is fibrous tissue (fig. 3), whereas only a small portion of the bundle of His in human beings is fibrous tissue.

Chemical Analysis.—One of us (A. E. O.¹⁵) undertook the development of a microchemical technic for the determination of glycogen by which quantitative and reproducible results could be obtained on tissues weighing about 10 mg. This we feel has been successfully accomplished, and all of the quantitative

15. Osterberg, A. E.: The Estimation of Glycogen in Small Amounts of Tissue, *J. Biol. Chem.* 85:97, 1929.

analyses for glycogen reported in this article were done by this procedure. The details of the technic, with proof of its quantitative nature, will be fully presented elsewhere and only a brief résumé given herein.

In a broad sense, the procedure was simply an application of microchemical technic to the Pflüger method, followed by the determination of dextrose by the new Folin microchemical method. A piece of tissue of appropriate size was quickly dissected out and placed in the bottom of a tarred glass-stoppered tube (6 by 100 mm.) containing 0.1 cc. of 60 per cent potassium hydroxide. The tissue was destroyed by heating in a steam bath at 100 C. for from two to three hours. For the precipitation of glycogen, 0.1 cc. of water and 0.4 cc. of alcohol were added; the contents were mixed by shaking and were allowed to settle for several hours. The tubes were then centrifugated, and the precipitate was washed successively by 0.3 cc. portions of 70 per cent alcohol, 95 per cent alcohol, 1:1 alcohol-ether mixture, ether and petroleum ether. Removal of the supernatant solutions was carefully carried out by pipetting off the solutions by means of a capillary pipet having a curved tip, which did not disturb the precipitate. After removal of the remaining petroleum ether in the steam bath, 0.5 cc. of six tenths-normal hydrochloric acid was added and the solution hydrolyzed for three

TABLE 1.—*Results of Chemical Analysis in One Heart of a Human Being**

Material	Time, p. m.	Weight, mg.	Colorimeter Reading	Glycogen, per Cent
Bundle of His.....	2:50	6.3	24.2	0.52
Cardiac muscle.....	3:00	8.2	18.1	0.52
Cardiac muscle.....	3:05	8.7	17.9	0.54
Cardiac muscle.....	3:10	9.5	14.2	0.58
Cardiac muscle.....	3:15	8.5	16.8	0.54
Cardiac muscle.....	3:20	6.2	22.8	0.56
Cardiac muscle.....	3:25	6.4	24.6	0.50
Average	0.54
Percentage difference between bundle and muscle = 3.8 per cent				

* The patient died at 11:10 a. m.; necropsy was performed at 2:00 p.m.

hours at 100 C. The entire solution or an aliquot portion, depending on the glycogen content, was transferred to a test tube graduated at 25 cc.; it was neutralized to litmus by the addition of 1 to 3 drops of fifth-normal sodium hydroxide, and the dextrose was estimated by the Folin microprocedure. A dextrose standard containing 0.03 mg. of dextrose was used.

RESULTS OF STUDY

Our material from twenty-one hearts of human beings was placed in 60 per cent potassium hydroxide at periods ranging from one hour and forty-five minutes to nine hours and fifty minutes after death. The result recorded for the cardiac muscle is the average of several estimations which checked closely. The value for the bundle of His was usually the result of only one estimation, because only a small amount of tissue was obtainable. The data in table 1 represent the results obtained in one case, which we took as a sample without reference to the figures.

Table 2 shows that the ratio of the percentage of glycogen in the muscle to that in the bundle of His of the twenty-one hearts of human beings varied between 1:0.50 and 1:1.17, if the one ratio of 1:1.75,

that apparently was an abnormal result, is excluded. Figure 4 shows the probability curve of these ratios exclusive of the one just mentioned. The ratios were plotted on arithmetic probability paper. The ordinate represents the ratio, and the abscissa the percentage of observations. The 50 per cent line crosses the ratio of 1:0.9; half the values were greater and half were less than this. This indicates that the probable average ratio is 1:0.9, or that there is a little less glycogen in the bundle than in the muscle. The figure also shows that 60 per cent of the results were between the ratios of 1:0.72 and 1:1.06.

Table 2 also shows that the amount of glycogen which remained in the cardiac tissues some time after death varies greatly. For instance,

TABLE 2.—*Comparison of Glycogen Content of the Muscle and of the Bundle of His of the Heart of Human Beings*

Case	Time Elapsed Between Death and Dissection		Glycogen in Muscle, per Cent	Glycogen in Bundle of His, per Cent	Ratio of Percent- age of Glycogen in Muscle and Bundle
	Hours	Minutes			
1	3	20	0.42	0.21	1:0.50
2	2	45	0.43	0.28	1:0.65
3	3	25	0.18	0.12	1:0.66
4	3	45	0.89	0.60	1:0.67
5	4	30	0.29	0.21	1:0.72
6	5	17	0.52	0.38	1:0.73
7	3	40	0.31	0.23	1:0.74
8	3	40	0.08	0.06	1:0.75
9	4	30	0.26	0.23	1:0.88
10	4	15	0.29	0.26	1:0.89
11	3	30	0.19	0.18	1:0.95
12	9	55	0.43	0.41	1:0.95
13	3	40	0.54	0.52	1:0.96
14	1	45	0.37	0.37	1:1.0
15	3	..	0.22	0.22	1:1.0
16	4	55	0.67	0.67	1:1.0
17	4	45	0.16	0.17	1:1.06
18	3	50	0.77	0.84	1:1.09
19	3	..	0.79	0.87	1:1.10
20	3	40	0.58	0.68	1:1.17
21	3	30	0.24	0.42	1:1.75

in case 14 the cardiac muscle and the bundle of His obtained one hour and forty-five minutes after death contained 0.37 and 0.37 per cent of glycogen, respectively. In case 12, the tissues obtained nine hours and fifty-five minutes after death, contained 0.43 and 0.41 per cent of glycogen. In case 8, in which the tissues were obtained three hours and forty minutes after death, the percentages of glycogen were 0.08 and 0.06.

A comparison of the salient data in table 3 of the cause of death and the cardiac lesion with the percentage of glycogen in table 2 does not show correlation between the cause of death or the condition of the heart, on the one hand, with the amount of glycogen in the cardiac tissues or with the ratio of percentage of glycogen in the cardiac muscle and in the bundle of His, on the other hand.

The hearts of four horses were studied in a similar manner, but with the difference that it was possible to obtain the tissues soon after the animals died. Three were shot through the frontal plate of the skull with a 0.22 caliber rifle and a fourth died from an unknown cause. Although the animals that were shot were bleeding from the cut carotid arteries, the hearts were removed and the desired tissues were quickly dissected out. An appreciable length of time after the first specimens were removed, others were taken and tested to determine whether

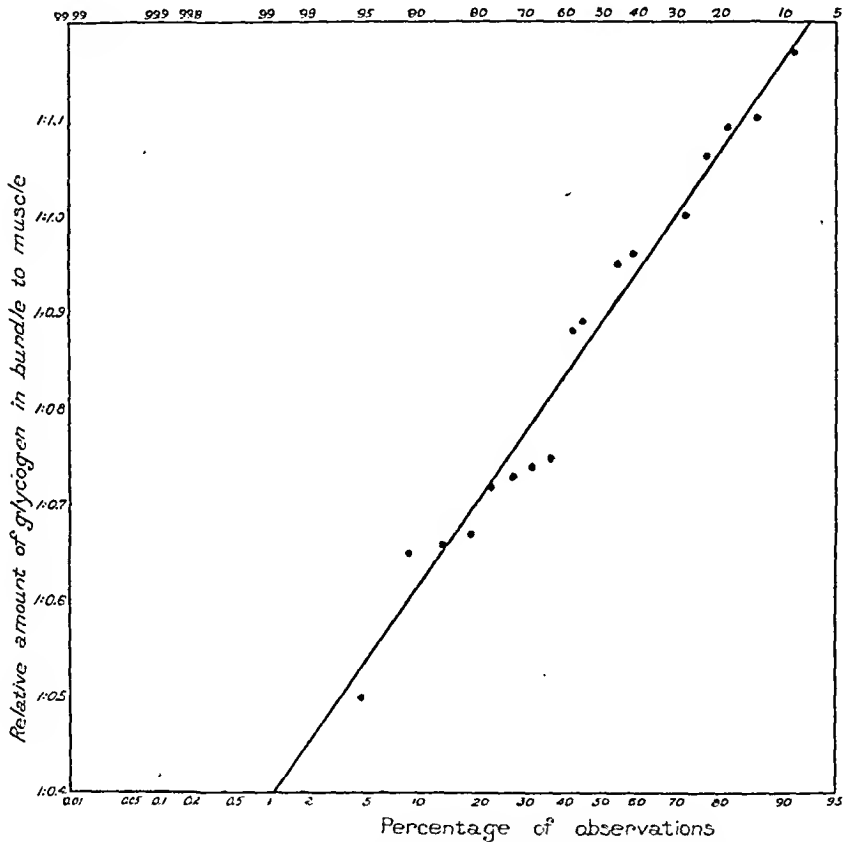


Fig. 4.—Probability curve of the ratio of the percentage of glycogen in the muscle to that in the bundle of His. The curve is based on results obtained from twenty hearts of human beings. The results in one of the twenty-one hearts were excluded because they were obviously abnormal. The ordinates represent the ratio; the abscissae, the percentage of observations.

any change had occurred in the ratio of glycogen in the muscle and in the conduction system. It was possible, because of the large size of the left bundle branch, to check the results of the estimation of the glycogen in two or more samples each time. The data are given in table 4.

It is seen that the tissue of the conduction system of the heart of the horse contains much more glycogen than the cardiac muscle, in spite of

TABLE 3.—*Salient Data Concerning Patients Whose Hearts Were Examined*

Case	Age, Years	Sex	Cause of Death	Cardiac Lesion
1	60	M	Cardiac decompensation with auricular fibrillation	Hypertrophy (702 Gm.); aortic stenosis; chronic infarction of left ventricle
2	59	M	Bronchopneumonia following prostatectomy	None
3	24	M	Subacute monocytic leukemia; cellulitis of left orbit and face, and cerebral abscess	None
4	65	M	Sudden death following years of dyspnea on effort	Coronary sclerosis with fibrosis of myocardium and dilatation of left ventricle
5	72	M	Septicemia following resection of carcinoma of rectum sixteen days before death	Terminal tricuspid vegetative endocarditis
6	75	M	Pyelonephritis and uremia following suprapubic cystostomy eleven days before death	Hypertrophy (543 Gm.) with hypertension basis
7	70	M	Uremia (chronic pyelonephritis) and myocardial degeneration; carcinoma of prostate gland	Hypertrophy (685 Gm.) with hypertension the probable basis
8	49	M	Pulmonary embolism eighteen days after compression of chest	None
9	37	M	General peritonitis following partial gastrectomy three days before death	None
10	64	M	Bronchopneumonia following exploration for carcinoma of stomach three days before death	Hypertrophy (462 Gm.); basis unknown
11	77	M	Sudden death thirteen days after suprapubic cystostomy; auricular fibrillation	Hypertrophy (430 Gm.); and dilatation; thrombosis of right auricular appendage
12	40	M	General peritonitis following ileocolostomy for carcinoma of cecum twelve days before death	None
13	47	F	General peritonitis following resection for carcinoma of rectum eight days before death	None
14	75	M	General peritonitis following exploration of carcinoma of colon three days before death	Coronary sclerosis
15	49	M	Acute pseudomembranous enteritis following gastro-enterostomy for duodenal ulcer three days before death	None
16	78	M	Emaciation from carcinomatous obstruction of cardia; myocardial degeneration (symptoms for four years)	Coronary sclerosis
17	40	M	Crushing of chest.....	Laceration and rupture of both auricles
18	51	M	Chronic healed hepatitis and pancreatitis (syphilitic?); cardiac decompensation	Hypertrophy (460 Gm.) and dilatation
19	30	F	Hepaticoduodenostomy for stricture of common bile duct eight days before death	Fatty degeneration (severe)
20	66	M	Cholecystostomy for obstructive jaundice from subacute pancreatitis seven days before death	None
21	76	M	Pyelonephritis with uremia following cystostomy for carcinoma of prostate gland twenty-two days before death; auricular fibrillation	Hypertrophy (470 Gm.)

TABLE 4.—*Comparison of Glycogen Content of the Muscle and of the Conduction System of the Heart of the Horse*

Horse	Mode of Death	Time Elapsed Between Death and Dissection		Glycogen in Muscle, per Cent	Glycogen in Conduction Tissue, per Cent	Ratio of Percentage of Glycogen in Muscle and Con- duction System
		Hours	Minutes			
1	Shot	30	0.42	1:1.95
		..	45	0.82	1:3.04
		2	35	0.26	1:5.44
2	Shot	22	0.32	1:5.96
		..	25	1.74	1:9.39
		1	25	0.30	1:10.10
3	Shot	1	25	1.79	1:4.63
		2	15	0.59	1:5.50
		1	50	5.54
4	Natural death.....	..	25	0.07
		..	30	0.71
		1	55	0.08
		1	55	0.37
		4	50	0.08
		5	35	0.44

the large amount of fibrous tissue present in the conduction system. The ratio varied from 1:1.95 to 1:10.10. This was surprising in view of the ratio obtained from the study of the hearts of human beings, in which, in spite of the small amount of fibrous tissue present in the specific system, the ratio varied from 1:0.50 to 1:1.17. It was even more surprising when compared with the results of Buadze and Wertheimer, whose ratios were just the reverse of ours.

The study of the glycogen content of the cardiac muscle and of the tissue of the conduction system of the hearts of horses at intervals after death showed that the glycogen disappeared rather slowly from these tissues. The results are equivocal in regard to which of the two types of tissue lose glycogen faster. The fact that the disappearance is slow, however, leads us to assume that the ratio determined for the hearts of human beings, a longer time after death, probably is not greatly different from the ratio existing soon after death.

COMMENT

We wish merely to report the results of our investigation of the ratio of glycogen in the muscle and in the tissues of the conduction system of the heart of the human being and of the heart of the horse as determined by a new microchemical technic. The results obtained are difficult to explain. Why in the heart of the horse there should be so much more glycogen in the conduction system than in the muscle whereas in the heart of the human being the percentage of glycogen in each of the two tissues is about the same, remains to be answered by further physiologic investigation. Neither can we explain the great discrepancy between the figures for the hearts of horses of Buadze and Wertheimer and ours, although we believe our method is more accurate and reliable.

SUMMARY

The ratio of percentage of glycogen in the muscle and in the tissues of the conduction system was determined by a new microchemical technic in twenty-one hearts of human beings and in four hearts of horses.

The ratio of percentage of glycogen in the muscle and in the bundle of His of the hearts of human beings varied between 1:0.50 and 1:1.17, with the probable average ratio of 1:0.9.

The ratio of percentage of glycogen in the muscle and in the radicles of the left bundle branch of the hearts of horses varied from 1:1.95 to 1:10.10, in spite of the much greater fibrous tissue content of the tissues of the conduction system in the horse.

Why there should be such a difference in this ratio between the heart of the human being and the heart of the horse cannot be explained at present.

Glycogen disappears slowly both from the cardiac muscle and from the tissues of the conduction system in specimens which are first studied within a half hour after death (hearts of horses), but the percentage of glycogen in the hearts (both of human beings and horses) varies markedly without any ascertainable reason.

EFFECT OF TONSILLECTOMY ON THE ACUTE ATTACK OF RHEUMATIC FEVER

PRELIMINARY REPORT *

WILLIAM H. ROBEY, M.D.

AND

MAXWELL FINLAND, M.D.

BOSTON

For a number of years the tonsils have been considered by many as an important focus in the persistence of rheumatic infections. It is likewise a well recognized fact among clinicians that acute attacks of rheumatic fever and recurrences of these attacks are frequently ushered in by acute infections of the tonsils. Tonsillectomy is therefore frequently recommended to the sufferers from this disease with the hope of preventing these recurrences. For the same reason we have for a number of years recommended enucleation of the tonsils during the acute attack of rheumatic fever in an attempt to determine whether or not a persistent infection could not be curtailed by removing this focus. We wish here to present briefly some of the results of our experience with this procedure over a period of five years.

In order to evaluate the effect of tonsillectomy as a therapeutic agent in the control of the acute attack of rheumatic fever, it was necessary to choose a group of patients that could be easily compared. For this purpose we have selected from the entire group of patients suffering from diseases now included under the name rheumatic fever all those admitted to the Second Medical Service of the Boston City Hospital between Jan. 1, 1924, and Dec. 31, 1928, because of an acute attack of rheumatic polyarthritis.

There were, in all, 165 patients. Of these, seventy-one were operated on during their residence for acute polyarthritis, leaving ninety-four as controls. Among the seventy-one operative cases there was definite clinical evidence of activity at the time of the operation in fifty, as shown in table 1; the remaining twenty-one cases were apparently quiescent. Some of our patients had previously been subjected to tonsillectomy, but about half of these had remains of tonsillar tissue (table 2). Sore throats and tonsillitis were apparently a larger factor in our

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* From the Second Medical Service, Boston City Hospital, and the Harvard Medical School.

operative cases than in those in which operation was not done (table 3). Active heart disease played a part in both groups, apparently more in the operative groups (table 4). This, and perhaps some of the comparisons later on, may depend on the severity of the cases chosen for operation, which may be judged from the fact that in these cases the ordinary medical treatment was tried without success for varying periods before operation was performed.

TABLE 1.—*Fifty Patients Operated on During the Active Stage of Acute Polyarthrits*

Evidence of Activity	Number of Cases
Acute disease of joints alone.....	18
Fever alone	4
Acute disease of joints and fever.....	20
Acute disease of joints and active cardiac lesion.....	2
Acute disease of joints, fever, and active cardiac lesion.....	5
Rever, active disease of joints, and pulmonary lesion.....	1
Total	50

TABLE 2.—*Number of Patients Subjected to Tonsillectomy Prior to Admission for Acute Polyarthrits*

Number of patients subjected to tonsillectomy prior to admission for acute polyarthrits.....	35
Number of those having tonsillar tissue evident on simple inspection of the throat at the time of entrance.....	17 or 48%

TABLE 3.—*Incidence of Sore Throats (Including Tonsillitis) in One Hundred and Sixty-Five Cases of Acute Polyarthrits During the Course of Joint Symptoms or Preceding Their Onset by a Period not Exceeding Fourteen Days*

Group	Cases in Patients Without Previous Tonsillectomy			Cases in Patients Previously Subjected to Tonsillectomy			Total		
	No. of Cases	With Sore Throat	Per Cent with Sore Throat	No. of Cases	With Sore Throat	Per Cent with Sore Throat	No. of Cases	With Sore Throat	Per Cent with Sore Throat
Operated on.....	64	46	72	7	4	57	71	50	70
Not operated on	66	24	36	28	11	38	94	35	37
Total.....	130	70	54	35	15	43	165	85	52

As a basis of comparison, we have chosen the data which appeared to us to be the simplest and most reliable, in view of the fact that all these patients received the same medical and nursing attention. The number of days of elevated temperature, the number of days of joint symptoms and the duration of the patient's stay in the hospital constitute definite objective data easily compared. At the time of entry the operative and control cases were readily comparable with regard to the duration of illness, information as to the number of days joint symptoms were present being the most easily obtainable and the most relia-

ble. In the hospital, however, the patients operated on are ill somewhat longer, as evidenced by the number of days of fever, the total duration of joint symptoms and the number of days of hospitalization. At the time of discharge the surgical patients were, on the whole, in better

TABLE 4.—*Evidence of Active Rheumatic Heart Disease While Under Observation*

	Operative Group			Unoperative Group		
	With Lesion at Entrance	Without Lesion at Entrance	Total	With Lesion at Entrance	Without Lesion at Entrance	Total
Easily accelerated rate, arrhythmias, disturbed conduction, decompensation...	5	3	8	8	3	11
Pericarditis, endocarditis, pancreatitis...	4	3	7	3	0	8
Total.....	9	6	15	11	3	14

TABLE 5.—*Time of Operation*

Number of Days from Time of Admission to Operation				Number of Days from Onset of Joint Symptoms to Operation			
Number of Days	Operation While Active	Operation While Quiescent	All Operative Cases	Number of Days	Operation While Active	Operation While Quiescent	All Operative Cases
7 or less.....	15	7	22	15 or less.....	7	4	11
8-15.....	17	5	22	16-30.....	17	8	25
16-30.....	8	6	14	31-60.....	19	8	27
31-48.....	10	3	13	61 or more.....	7	1	8
Total cases...	50	21	71	Total cases...	50	21	71
				Operation While Active	Operation While Quiescent	All Operative Cases	
Average number of preoperative days in the hospital.....				16	15	16	
Average number of days from onset of joint symptoms to operation				37	30	35	

TABLE 6.—*Duration of Joint Symptoms at Time of Entrance*

Number of Days	Operative Group	Unoperative Group
1-7.....	26	29
8-14.....	12	22
15-31.....	21	30
32-63.....	8	10
64 +.....	4	3
Average Duration Prior to Entrance		
Operative cases.....	19 days	Unoperative cases..... 19 days

condition. The three deaths were in patients who died after a brief stay from complications indicated in table 10. They can readily be excluded from the comparison. The actual figures are shown in tables 6 to 10.

The results of the operation are summarized in table 11. The accompanying graphic records of three cases will illustrate some of the

TABLE 7.—*Duration of Fever and of Hospitalization in Operative Cases*

Number of Days of Elevated Temperature (in Hospital)	Number of Cases			Number of Days in Hospital	Number of Cases *		
	Operation While Active	Operation While Quiescent	Total		Operation While Active	Operation While Quiescent	Total
Afebrile throughout.....	6	2	8	15 or less.....	4	7	11
1-7	21	15	36	16-30.....	16	6	22
8-15.....	11	3	14	31-60.....	22	7	29
16-30.....	7	1	8
31 or more.....	5	0	5	61 or more.....	8	1	9
All cases.....	50	21	71	All cases.....	50	21	71
				In Operative Cases While Active	In Operative Cases While Quiescent	In All Operative Cases	In Un-operative Cases
Average number of days of elevated temperature (in hospital).....				12	5	10	8
Average number of days in hospital.....				40	28	38	25

TABLE 8.—*Total Duration of Joint Symptoms*

Number of Days	Operative Cases	Unoperative Cases
15 or less.....	6	18
16-30.....	26	32
31-60.....	26	26
61-90.....	9	14
91 or more.....	4	4
Average Duration of Joint Symptoms		
Operative cases..... = 40	Unoperative cases..... = 36	

TABLE 9.—*Number of Days in Hospital*

Number of Days	Operative Cases	Unoperative Cases
15 or less.....	11	35
16-30.....	22	31
31-60.....	29	23
61 or more.....	9	5
Average Sojourn in the Hospital		
Operative cases..... = 38 days	Unoperative cases..... = 25 days	

TABLE 10.—*Condition at Time of Discharge*

	Operative Cases	Unoperative Cases	Operative and Unoperative
Well	50	60	110
Symptom-free; discharged for further convalescence elsewhere.....	19	21	43
Unimproved; disease still active.....	2	7	9
Dead	0	3*	3
Total number of cases.....	71	91	165

* Two deaths due to pneumonia and one to pulmonary infarction.

TABLE 11.—*Effect of Operation on the Acute Attack*

	Number of Cases
Operation; marked onset of improvement.....	16
Operation apparently accelerated improvement.....	8
No apparent effect on course.....	9
Caused definite exacerbation of symptoms.....	13
Apparently good immediate result with early recurrence.....	4
Postoperative hemorrhage or pulmonary complications.....	0
Complications in Twenty-One Quiescent Operative Cases	
Mild flare-up of symptoms.....	4
Moderate flare up.....	4
Severe sore throat.....	1
Postoperative hemorrhage.....	1

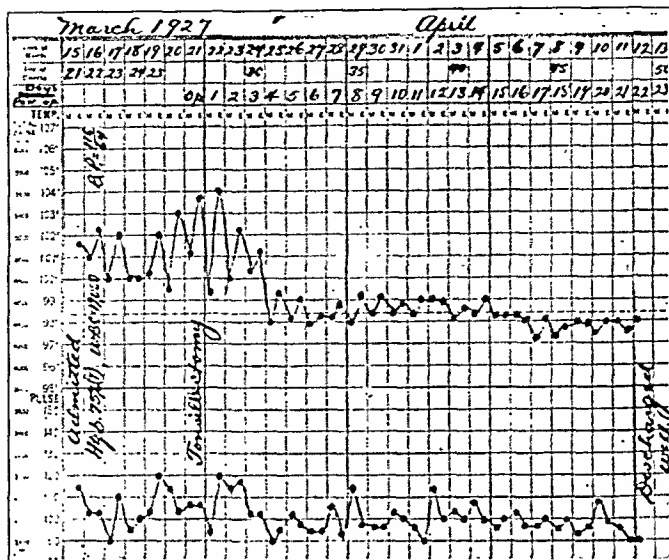


Chart 1.—Peritonsillar abscess one month before entry, in M. S., a man, aged 27. Drained and improved in one week. Throat remained slightly sore and multiple acute joint symptoms began. Heart normal at the time of operation. Joints remained acutely inflamed without relief from salicylates in doses of 1.2 Gm. every four hours. An operation was done under local anesthesia and improvement began the day after operation. The joints were clear and the patient entirely symptom-free after three days.

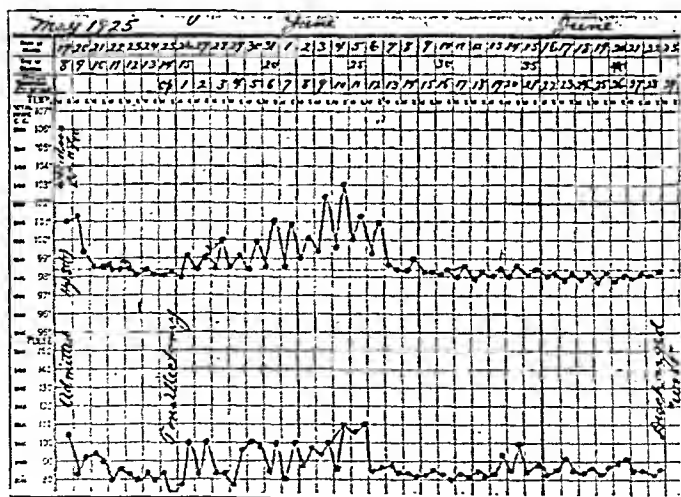


Chart 2.—Sore throat and chest cold for one month prior to entry in E. H., a woman, aged 18. Multiple acute joint symptoms began with sore throat, May 12, 1925; no previous rheumatic history. Symptom-free after two days with salicylates. Symptom-free at time of operation. Flare-up of joint symptoms following operation, June 10. Thereafter symptom-free.

features mentioned. The legends accompanying the charts give the essential details of the history. Three types of results are exemplified here. The third case represents the commonest reason for poor results following tonsillectomy, namely, incomplete removal at the first operation.

Tonsillectomy has been performed sporadically for a number of years in acute rheumatic fever, but there has not been a general acceptance of the procedure because of a reluctance to subject patients with fever and acutely inflamed joints to operation. The general tendency of our profession is to wait until the temperature, joint symptoms and leukocytosis have quieted down, but during that delay there is increasing danger to the heart and economic loss. That a recurrence of rheumatic fever increases the probability of cardiac damage is apparent from table 13. The question of tonsillectomy as a preventive of subsequent

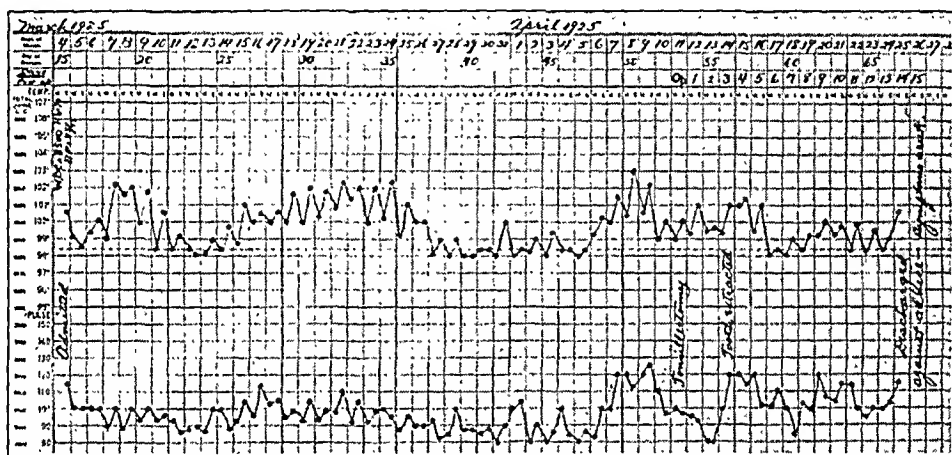


Chart 3.—Previous rheumatic fever in childhood and in 1923. J. F., a woman, aged 20, was admitted for multiple acutely inflamed joint symptoms of fourteen days' duration. Sore throat, Feb. 25, 1925, and frequently for previous three years. Tonsillectomy was performed in 1914; tabs were seen on entry. Sharp pre-cordial pain and dyspnea had been present for two days. Heart normal on examination. Before operation no relief was obtained with salicylates in doses of 2 Gm. every four hours. After operation the patient was not improved but insisted on discharge.

attacks of rheumatic fever has been much studied, is not yet settled and will not be considered here, except tentatively in table 12, which indicates the relation of tonsillectomy to the occurrence and recurrence of acute polyarthrititis. It would seem from a study of these figures that an initial attack or a recurrence may take place after tonsillectomy. How much the type of operation has to do with this fact is difficult to evaluate, except that it may be surmised from table 2 that the original operation on those patients having attacks after removal of the tonsils was not entirely successful from the surgical point of view. It should

be noted, however, that even those authors who emphatically deny the value of tonsillectomy usually head their list of the causes of acute polyarthritis with infected tonsils. Many who believe in tonsillectomy prefer to wait until the fever and inflamed joints have quieted down. Such was formerly our plan, but that has been changed in the last five years for the reasons that we have stated. From the economic standpoint the hospital has not yet profited, since our tables show that surgical patients averaged a longer time in the wards than the nonsurgical patients. The reasons for this were the delays in arriving at the point for operation, the number of days afterward during which the patient was kept while we assured ourselves that the procedure had been a success, and, most important, the greater severity of the conditions

TABLE 12.—*Relation of Tonsillectomy to the Occurrence and Recurrence of Acute Polyarthritis*

Number of patients admitted for their first attack of polyarthritis	87
Same, subsequent to tonsillectomy.....	24, or 28%
Number of patients admitted for a recurrence of acute polyarthritis	78
Same, subsequent to tonsillectomy.....	11, or 14%
Total number of patients with acute polyarthritis.....	165
Number of these previously subjected to tonsillectomy.....	35, or 21%

TABLE 13.—*Relation of History of Previous Attacks of Rheumatic Fever or Chorea to the Presence of Rheumatic Heart Disease on Admission in One Hundred and Sixty-Five Cases of Acute Polyarthritis*

Number of patients having rheumatic heart disease at the time of entrance	63, or 39%
Number of patients admitted for first attack of acute polyarthritis.....	87
Number of these having rheumatic heart disease at time of entrance.....	24, or 28%
Number of patients admitted for a recurrence of acute polyarthritis.....	78
Number of these having rheumatic heart disease at the time of entrance....	39, or 50%

in patients operated on. The mild cases generally respond readily to the usual medical treatment.

CONCLUSIONS

The initial physical examination of any patient with acute rheumatic fever should include a thorough search for the foci of infection. The earlier the focus of infection is discovered, the greater the possibility of removing it, thus lessening the recurrence of attacks, the length of time in the hospital and the danger of cardiac involvement. When attention is given to this treatment, the removal of the focus can be performed as readily at the end of one week as four.

We feel that we have presented evidence that tonsillectomy may be performed during the active stage of acute rheumatic fever without harm to the patient from the operation. Tonsillectomy at this time

offers no more dangers than when performed under what appear to be the most favorable conditions.

Ether was the anesthetic selected for the majority of our cases.

The only complication that delayed operation was an accompanying bronchitis or bronchopneumonia. Cardiac conditions practically never contraindicate operation except in extreme cases.

Patients who have had recurrences under the usual medical treatment, and are operated on during the quiescent stage, should be told that the tonsillectomy may produce an exacerbation of the joint symptoms, but that it will probably be mild and brief if the operation is a success.

The decision to operate was made by internists and not by rhinologists. The operation should be done only by experienced persons, since failure to enucleate the diseased tonsils completely leaves the patient in as dangerous a condition as before and throws discredit on the procedure as a preventive of acute polyarthritis and rheumatic heart disease.

We unhesitatingly offer tonsillectomy as a safe therapeutic measure for those patients particularly who fail to respond to the ordinary medical measures. In several cases in which symptoms have repeatedly recurred, the results of operation have been brilliant.

ABSTRACT OF DISCUSSION

DR. S. MARX WHITE, Minneapolis: We are all interested in lessening the incidence of the results of rheumatic fever, such as involvement of the heart. We have often seen a child come to the hospital immediately following a tonsillectomy, done more or less skilfully, said by the family to be distinctly worse than it was before the operation. Drs. Robey and Finland, with their skilled staff of assistants and with the skilled rhinologist, have been able to secure results which interest us greatly.

A number of years ago, when irradiation of the tonsil was presented as a means of sterilizing that organ, we attempted to carry out the procedure, but were not long in becoming convinced that no sterilization of the tonsil could be performed by means of the x-ray or any other agent that left the tonsil in situ. We became aware, however, that the x-ray could cause shrinkage of the lymphoid tissue in the tonsil, even an acutely inflamed one, and that by shrinking the tonsil with the x-ray preliminary to its removal, we might achieve something. One case of rather acute severe exacerbation following tonsillectomy led us to be very cautious. Dr. Robey's study should not lead, as yet, to the generalized adoption of tonsillectomy during acute rheumatic fever, particularly on the advice of the rhinologist.

DR. FRANK SMITHIES, Chicago: What relationship has existed in these cases between the bacteriology of the tonsils and the blood cultures and of cultures made from joint fluids at the time when the patient was having febrile exacerbations? It seems to me that by investigating along these lines, more information might be secured and this would guide our line of procedure. Certainly, in some of the instances cited, it would appear that one is dealing with bacteremias as

causes of fever or that there are active bacterial growths in joint fluids wholly irrespective of the local tonsil condition.

DR. F. M. POTTENGER, Monrovia, Calif.: I should like to discuss the authors' paper in connection with Swift's idea of acute articular rheumatism being an allergic manifestation. The temperature charts shown by Drs. Robey and Finland may be duplicated in tuberculosis. If I did not know that these charts represent streptococcic infections, I could explain them just as well as allergic reactions in tuberculosis. I see phenomena in the tuberculosis clinic comparable to those the authors mentioned. For instance, in a patient with a severe tuberculosis of one lung, and a lesser lesion in the other, both being active, if a large reinoculation either of bacilli or of bacillary protein takes place from some one area of infection, a marked reaction will take place at the point of implantation, but a milder reaction may appear in all unhealed lesions in both lungs. In such a case, if pneumothorax is done on the side of the severe lesion, the other lung goes on to a cure. If, on the other hand, there are major reinoculations taking place from the other lung as well, then collapsing the one will not stop the activity. This is comparable to removing a tonsil when reinoculations are taking place from it and keeping up an allergic reaction in an infected joint. I had a patient who had a severe tuberculosis of the right lung, and a lesion in the kidney. The lung improved markedly but was quickly made the seat of an inflammatory exudative allergic reaction by tuberculo-protein, which was set free in the blood stream by a focus in the kidney. The same situation is often seen in diseases of the larynx and bowels. Another interesting condition that is comparable to what is seen in rheumatism is a sudden infection of a testicle, which takes place at times when the lungs are involved. This is due to the fact that testicular cells are highly sensitized, and when tubercle bacilli become implanted they stir up an immediate allergic reaction. The tissues become edematous, if the inoculation is small, after a few days the edema begins to disappear and there is a slow return to normal. If the numbers of bacilli are larger, necrosis with destruction takes place and a sinus persists. As a part of the immunologic process in streptococcal infection there is a sensitization similar to that in tuberculosis. So when bacilli gain access to the blood stream and become implanted in a heart valve, or in a joint, an allergic reaction takes place which differs according to the tissue involved. In some instances there will be only a slight hyperemia and a mild exudation, proliferative phenomena predominating, while in others there is a marked exudation with a pouring out of serum, and sometimes cells and fibrin. One can readily see the difference in reaction that would take place in the joint and in the heart valves. It seems to me that all the phenomena described by Drs. Robey and Finland can be best understood on the basis of sensitized cells in the presence of reinoculations of bacteria or bacterial products. The streptococci gain access to the blood stream and produce new implantations in the joints or in the heart, after which either the streptococci or the products derived from them, gaining access to the blood stream, will keep up an allergic reaction in whatever tissues infection has been established. If the focus giving out the material for reinoculation is removed, the source of the material causing an allergic reaction is removed. If, however, the organ or part removed does not prove to be the source, the situation has not been relieved. During the removal of the infected organ, many bacteria or bacterial products might be thrown into the blood stream and produce another violent reaction, thus the operation itself produces violent symptoms.

DR. RUSSELL L. CECIL, New York: During the past year at Bellevue Hospital we have been able to obtain positive blood cultures (streptococci) from about 80 per cent of our patients with rheumatic fever. In five out of seven joint punctures, we have also obtained streptococci. This work corroborates previous studies by Poynton and Payne, Rosenow, and others. If it is true that this disease is a streptococcal infection and that streptococci are emanating from the tonsils or the throat, it behooves us to eliminate these foci as quickly as possible, perhaps by taking out the foci during the acute stage of the disease if the tonsil is not too acutely inflamed. I wish the authors would tell us how these tonsils looked at the time of operation. If the attack of tonsillitis and sore throat occurred two weeks before the rheumatic fever, that would enable the laryngologist to do his work without flooding the system with too many additional streptococci. If only a few more should escape during tonsillectomy, I suppose it would not do much harm. The crux of the matter is in the condition of the tonsil at the time operation is undertaken. So far as the patient's symptoms are concerned, there is reason to believe that if these tonsils can be taken out and this source of bacteremia removed, the condition in the joints will clear up more promptly. We know that, as a rule, streptococci are easily overcome in the joints. This is shown by the migratory character of the joint symptoms, so if we can get foci removed promptly, we might save the heart some injury and save the patient's time, too. Perhaps the future treatment of rheumatic fever will be prompt removal of foci during the first attack and then prophylactic vaccination every spring with the patient's own streptococcus against recurrence. In that way we might be able to save the patient from the second, third and fourth attacks, which produce additional injury to the heart valve.

DR. WILLIAM H. ROBEY, Boston: In answer to Dr. White, we have not tried the method of irradiation. Although I know the tonsil may be shriveled with one treatment, still I have always felt that there might be enough infected crypts left to give poor results. Since we have not had bad effects from enucleation, I feel inclined to go on with that method. I knew that somebody would raise the question, as Dr. Smithies has, concerning bacteriology. We have been making some studies, but the whole subject is so chaotic that I do not want to go into it. We are taking out the tonsils because we think they are involved, and we are leaving the bacteriology for the present to other investigators. This is merely a preliminary report, and we hope to consider the bacteriologic aspect a little later. Dr. Cecil asked what the tonsils looked like. That is a difficult question to answer. First of all we try to discover what foci are present in teeth or tonsils, but in the cases in which we have operated, naturally we have ruled everything out, with the exception of the tonsils. Usually, there is a history of repeated attacks of sore throat. There is often the history of an attack some time before, and then the attack which, as Dr. Cecil says, occurs often two weeks before the acute rheumatism comes on, and the tonsil looks inflamed or contains something resembling pus which can be squeezed from it. There is a great deal of dissension as to what can be squeezed from it, since the dissenters say that when one obtains what looks like pus, it perhaps is not pus at all. A patient of that type was sent to me by a surgeon because he saw nothing about his operation that could have produced acute rheumatism, yet the woman, who was 44 years of age and apparently in good condition, had a muscular rheumatism which was persisting and moving about in the various muscles and which was alarming her greatly because she had an important business position and was much afraid that she was going to become incapacitated. I looked into her throat and saw that

the right tonsil was larger than the left, and I could, by pressing on it, squeeze something out of the crypts. I sent her to one of our leading throat men, who said that he saw no reason for taking out the tonsils, but I insisted that, in view of an otherwise negative physical examination, tonsillectomy should be performed. He took out the tonsils and was generous enough to send word to me that he thought he had made a mistake, because when he got into the tonsils he found that they actually did contain pus. I do not think anybody knows exactly what kind of tonsil to take out, but if there has been a history of repeated sore throat and the tonsils look as if they were diseased and no other focus can be found, I think they should be removed. That is the history on which we have gone in these seventy-one cases in which we have operated.

PANCREATIC FUNCTION

V. THE SECRETORY MECHANISM OF DIGESTIVE JUICES*

SEIZABURO OKADA, M.D.

KWANICHI KURAMOCCHI, M.D.

TOSHIO TSUKAHARA, M.D.

AND

TATSUO OOINOUE, M.D.

TOKYO, JAPAN

In the foregoing paper¹ we noted that hypoglycemia provokes the gastric, pancreatic and biliary secretions, and that hyperglycemia inhibits these. Since hypoglycemia induces humorally an excitatory impulse and hyperglycemia an inhibitory impulse to the secretory center, since from this center the stimulus and the inhibitory impulse are transmitted through the autonomic nervous system to the acting tissue cells, and since this phenomenon plays an important rôle as a regulatory mechanism in the process of gastric, pancreatic and biliary secretion, we called this phenomenon the "humoroneural regulation of the secretion of digestive juices." It is proved that the salivary secretion is excepted from this regulation. Furthermore, in dogs provided with a Thiry-Vella fistula, the secretion of the intestinal juice does not show this regulatory mechanism. It is well known that the alimentary hyperglycemia is usually due to the increase of dextrose in the blood. Therefore it is of interest to know whether other kinds of sugar have a similar effect on the secretory mechanism of gastric, pancreatic and biliary glands when introduced directly into the circulatory system. As the researches of Heidenhain, Hamburger, Höber and Cohnheim,

* Submitted for publication, Oct. 4, 1929.

* From the Medical Clinic of Prof. R. Inada, Imperial University of Tokyo.

* This and the foregoing papers refer not only to the pancreatic function but also to the secretory functions of the whole glands of the digestive tracts, so that the title "Pancreatic Function" does not cover the whole contents of the researches. Still we feel it rather fair to keep this title to show the origin of these works.

* Preliminary reports were: Studies on the Mechanism of the Secretion of Digestive Juices (in Japanese) *Nippon Naikagakkai Zasshi* **17**:106 (May 10), 1929; abst. in English, *ibid.*, June 10, 1929; The Humoroneural Regulation of the Secretions of the Digestive Organs: II. Report, *Proc. Imperial Acad. Tokyo* **6**:18 (Jan.) 1930.

1. Okada, S.; Kuramochi, K.; Tsukahara, T., and Ooinoue, T.: Pancreatic Function: IV. The Humoroneural Regulation of the Gastric, Pancreatic and Biliary Secretions, *Arch. Int. Med.* **43**:446 (April) 1929.

from 1894 to 1899, proved that the hypertonic and hypotonic solutions become nearly isotonic when resorption occurs in the small intestine, it seems reasonable to use isotonic solutions, administered parenterally, to imitate the natural process as far as possible. We chose the change in the acidity of the gastric juice as the main indication of the effect of the sugar administered. The gastric contents were collected continually by suction, and every fifteen minutes a specimen was separately determined. Usually 200 cc. was injected into the cubital vein. As the isotonic solutions, 5.6 per cent of monosaccharides and 11.2 per cent of disaccharides were used. All methods applied that are not described here were given in previous papers.

It was found that dextrose invariably causes a distinct diminution of the acidity of the gastric juice, often accompanied by a diminution

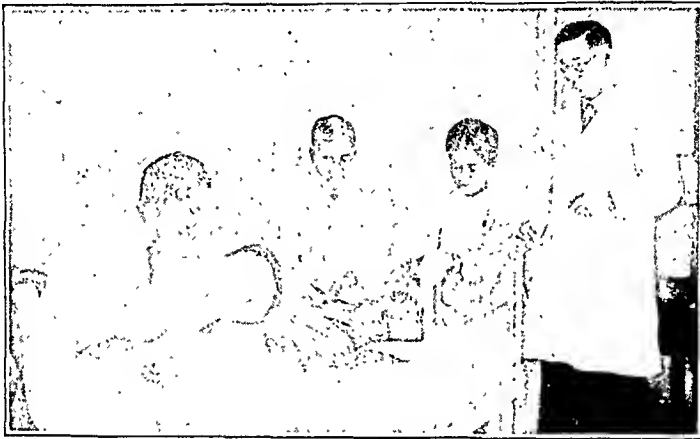


Fig. 1.—Scene showing the method of research: Kuramochi is performing an intravenous injection assisted by a nurse; Ooinoue is ready with a Hagedorn pipet for a sample of blood; Okada is collecting the duodenal return and controlling the whole procedure; another nurse is collecting the gastric juice.

of the amount. Maltose has a similar effect, but the diminution of the acidity tends to occur somewhat later. Levulose and galactose sometimes cause a diminution of the acidity, while at other times they show almost no effect. This divergence in effect is due probably to the fact that the amount of these two sugars in some cases is sufficient to cause an inhibitory stimulation of the center while in others it is insufficient. Lactose and sucrose produced no apparent effect. The first (fifteen minutes) specimen is often uninfluenced or is even increased in acidity or in amount when dextrose is injected, owing to the fact that a reaction of the humoroneural mechanism requires a certain time to develop. The second (thirty minutes) specimen usually shows a distinct reactive diminution. When maltose is used, this diminution occurs usually in the third (forty-five minutes) specimen. After prolonged suction (one hour or more) a diminution of the acidity or of the

amount may also occur, even when lactose or sucrose is used, but this cannot be attributed to the direct effect of that sugar. This problem is being studied by one of us (K. K.) on dogs with permanent pancreatic fistula. This study also proves that the foregoing relation to the pancreatic secretion exists. In this respect it might be justifiable to recall the remarkable researches of Mann and Magath² as well as that of Noble and Macleod.³ Mann and Magath conclusively proved that the total removal of the liver is always followed immediately by a progressive decrease in the sugar content of the blood and that the development of the characteristic symptoms, which quickly lead to death, exactly

TABLE 1.—*Results of the Analyses of the Saliva Following the Intravenous Injection of 200 Cc. of 25 per Cent Dextrose in a Man, Aged 19*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Saliva, Cc.	Degree of Amylolytic Activity, Units	Amount x Amylolytic Activity, Units
Fasting				
1/4	7.0	1,380	9,660
1/2	0.099	7.8	1,286	10,031
3/4	7.2	852	6,134
1	0.102	5.6	1,046	5,858
Following an Injection of Dextrose				
1/4	0.444	2.5	1,754	4,385
1/2	0.266	6.4	1,266	8,102
3/4	0.150	7.0	1,622	11,354
1	0.109	9.0	928	8,352
1 1/4	0.090	3.6	928	3,341
1 1/2	0.077	4.0	1,206	4,824
1 3/4	0.084	4.2	1,864	7,829
2	0.079	3.6	1,434	5,162
2 1/4	0.075	4.4	2,046	9,002
2 1/2	0.077	4.8	1,574	7,555
2 3/4	0.077	4.0	2,014	8,056
3	0.081	5.0	1,864	9,320
3 1/4	0.084	5.0	1,982	9,910
3 1/2	0.089	3.2	2,468	7,898
3 3/4	0.085	2.8	1,648	4,614
4	0.090	2.4	1,808	4,339

parallel this decreasing blood sugar level. Intravenous administration of dextrose never failed to restore to normal an animal that had developed the group of symptoms associated with a low blood sugar level. In other experiments, dextrose was administered either by mouth, by rectum, by jejunostomy, by continuous intravenous injection or intraperitoneally immediately after hepatectomy; in none in which a normal blood sugar value or a hyperglycemia was maintained successfully, did the first characteristic group of symptoms develop. Mann and Magath

2. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: II. The Effect of the Removal of the Liver on the Blood Sugar Level, *Arch. Int. Med.* **30**:73 (July) 1922; III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, *ibid.* **30**:171 (Aug.) 1922.

3. Noble, E. C., and Macleod, J. J. R.: The Influence of Sugars and Other Substances on the Toxic Effects of Insulin, *Am. J. Physiol.* **64**:547, 1923.

TABLE 2.—*Results of the Analyses of the Saliva Following the Intravenous Injection of 200 Cc. of 5.6 per Cent Dextrose in a Man, Aged 39*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Saliva, Cc.	Degree of Amyolytic Activity, Units	Amount × Amyolytic Activity, Units
Fasting				
1/4	2.9	1,934	5,609
1/2	0.081	2.4	1,310	3,144
3/4	4.5	1,536	6,912
1	0.080	3.9	1,148	4,477
Following an Injection of Dextrose				
1/4	0.170	6.5	1,536	9,934
1/2	0.090	6.9	1,272	8,777
3/4	0.071	6.5	1,310	8,515
1	0.074	5.1	1,114	5,681
1 1/4	0.078	4.3	1,388	5,963
1 1/2	0.081	5.5	1,182	6,501
1 3/4	0.080	4.7	1,082	5,085
2	0.080	3.7	1,330	4,921
2 1/4	0.081	5.0	1,200	6,000
2 1/2	0.083	4.9	1,200	5,880
2 3/4	0.081	4.7	1,082	5,080
3	0.081	5.0	1,050	5,250
3 1/4	0.078	5.0	860	4,300
3 1/2	0.080	2.7	1,182	3,191
3 3/4	0.080	4.9	1,182	5,547
4	0.078	4.0	1,348	5,392

TABLE 3.—*Intestinal Secretion Following the Hypodermic Injection of Insulin and Dextrose **

A. Dog 6, female, weighing 14.5 Kg.; experiment done five days after a Thiry-Vella fistula was made			B. Dog 8, female, weighing 15.8 Kg.; experiment done seven days after a Thiry-Vella fistula was made		
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Intestinal Juice, Cc.	Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amount of Intestinal Juice, Cc.
	Fasting			Fasting	
1/4	1.6	1/4	0.7
1/2	0.097	2.6	1/2	0.087	0.7
3/4	2.3	3/4	1.0
1	0.099	2.2	1	0.081	1.0
Following an injection of 20 units of insulin hypodermically			Following an injection of 30 units of insulin hypodermically		
1/4	0.092	2.3	1/4	0.073	2.7
1/2	0.077	2.5	1/2	0.060	0.8
3/4	0.063	2.3	3/4	0.037	0.5
1	0.061	2.6	1	0.033	1.1
1 1/4	0.057	2.7	1 1/4	0.036	0.2
1 1/2	0.053	2.9	1 1/2	0.036	0.4
1 3/4	0.051	2.9	1 3/4	0.033	0.3
2	2.0			
Following an injection of 300 cc. of 5.6 per cent dextrose, hypodermically			Following an injection of 300 cc. of 7 per cent dextrose hypodermically		
1/4	0.053	1.5	1/4	0.083	1.2
1/2	0.079	1.0	1/2	0.100	2.2
3/4	0.088	1.2	3/4	0.094	1.7
1	0.093	0.9	1	0.096	0.9
1 1/4	0.091	1.3			
1 1/2	0.091	1.3			

* Elastic cannulas were inserted into the fistulas during collections.

further attempted to determine whether the reactive action of dextrose in the moribund condition following hepatectomy was specific. For this purpose, a wide variety of substances which seemed to have a related action were tested in the same manner and in amounts which

TABLE 4.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 5.6 per Cent Dextrose in a Man, Aged 19*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	24	33	12.0
1/2.....	0.090	36	45	21.0
3/4.....	40	49	19.0
1.....	0.086	49	62	5.6
Following an injection of dextrose				
1/4.....	0.157	54	63	5.0
1/2.....	0.108	19	30	9.4
3/4.....	0.075	27	41	5.5
1.....	0.081	25	38	8.0
1 1/4.....	0.088	31	42	4.2
1 1/2.....	0.083	23	42	6.6
1 3/4.....	0.081	35	47	3.0
2.....	0.081	67	79	5.8
2 1/4.....	0.079	89	99	7.0
2 1/2.....	0.084	88	100	1.8
2 3/4.....	0.086	94	104	4.6
3.....	0.084	83	100	7.0

TABLE 5.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 11.2 per Cent Maltose in a Man, Aged 24*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	32	37	17.0
1/2.....	0.100	59	66	11.0
3/4.....	53	60	7.2
1.....	0.094	32	41	9.0
Following an injection of maltose				
1/4.....	0.194
1/4.....	49	54	7.5
1/2.....	0.160
1/2.....	0.151	45	50	8.3
3/4.....	0.135	28	34	1.4
1.....	0.131	30	33	1.0
1 1/4.....	0.121	10	22	1.1
1 1/2.....	0.111	4	14	8.5
1 3/4.....	0.114	5	14	1.2
2.....	0.110	6	16	1.1
2 1/4.....	0.108	16	27	2.0
2 1/2.....	0.110	2	15	2.4
2 3/4.....	0.112	20	26	7.5
3.....	0.107	22	30	7.0

seemed to correspond to the amount of dextrose necessary to restore the hepatectomized animal to normal. The following substances tested were found not to have a restorative action: Saccharose, lactose, levulose, inulin, sodium chloride, sodium sulphate, sodium carbonate, sodium

bicarbonate, ethyl alcohol, glycerin, lactic acid (racemic), acetic acid, hydrochloric acid, pyruvic acid, epinephrine, pituitary extract and glycocoll. Only four substances were found, besides dextrose, which had

TABLE 6.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 5.6 per Cent Levulose in a Man, Aged 24*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	42	51	5.4
1/2.....	0.098	28	36	4.0
3/4.....	34	43	1.1
1.....	0.109	54	61	2.2
Following an injection of levulose *				
8 minutes.....	0.142
1/4.....	0.123	40	50	1.1
1/2.....	0.102	19	28	2.2
3/4.....	0.098	18	30	4.0
1.....	0.104	16	28	0.8
1 1/4.....	0.102	26	40	2.5
1 1/2.....	0.098	48	59	9.5
1 3/4.....	0.098	83	90	13.6
2.....	0.098	84	91	8.8
2 1/4.....	0.096	90	98	4.4
2 1/2.....	0.095	67	74	3.0
2 3/4.....	0.098	35	49	1.1
3.....	0.094	48	58	1.1

* Sometimes no diminution of the gastric acidity was observed after an injection of levulose.

TABLE 7.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 5.6 per Cent Galactose in a Man, Aged 19*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity†	Amount of Juice, Cc.
Fasting				
1/4.....	27	35	12.8
1/2.....	0.084	42	53	9.6
3/4.....	38	49	7.8
1.....	0.079	36	47	9.0
Following an injection of galactose *				
1/4.....	0.143	74	84	16.2
1/2.....	0.095	75	83	24.6
3/4.....	0.086	63	71	8.0
1.....	0.090	63	72	4.4
1 1/4.....	0.088	66	74	8.6
1 1/2.....	0.088	51	59	8.0
1 3/4.....	0.088	33	40	9.2
2.....	0.086	34	42	9.2
2 1/4.....	0.091	23	31	4.4
2 1/2.....	0.091	35	44	7.2
2 3/4.....	0.090	40	51	16.6
3.....	0.088	70	79	12.6

* Sometimes a diminution of the gastric acidity was observed after an injection of galactose.

† Although no diminution of the acidity is shown in this case, it sometimes occurs.

a beneficial action when injected into the moribund animal with a low blood sugar level following removal of the liver. These were maltose, mannose, dextrin and galactose. Noble and Macleod carried out careful

experiments on rabbits with insulin convulsions and obtained the following results: The only sugar which can definitely serve as an antidote to the symptoms that accompany the hypoglycemia due to insulin is dextrose. Even when the animal is moribund at the time of injection

TABLE 8.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 11.2 per Cent Lactose in a Man, Aged 24*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	18	23	4.6
1/2.....	0.095	12	22	2.0
3/4.....	20	32	2.2
1.....	0.097	23	36	13.4
Following an injection of lactose				
8 minutes.....	0.145
1/4.....	0.137	33	43	19.0
1/2.....	0.119	36	45	10.0
3/4.....	0.112	34	42	4.2
1.....	0.105	33	42	9.4
1 1/4.....	0.098	50	53	1.1
1 1/2.....	0.093	40	50	1.6
1 3/4.....	0.095	33	47	3.0
2.....	0.098	30	40	1.3

TABLE 9.—*Results of the Analyses of the Contents of the Stomach Following the Intravenous Injection of 200 Cc. of 11.2 per Cent Sucrose in a Man, Aged 19*

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	54	65	20.0
1/2.....	0.098	66	76	11.0
3/4.....	56	66	11.0
1.....	0.091	65	77	31.0
Following an injection of sucrose				
1/4.....	0.089	69	78	18.0
1/2.....	0.093	71	80	17.8
3/4.....	0.089	66	72	10.6
1.....	0.086	58	67	12.0
1 1/4.....	0.089	77	88	7.0
1 1/2.....	0.084	43	53	13.0
1 3/4.....	0.087	42	51	9.0
2.....	0.089	41	48	5.2
2 1/4.....	0.086	60	66	14.0
2 1/2.....	0.084	61	74	26.5
2 3/4.....	0.084	60	67	16.0
3.....	0.082	63	71	13.2

this sugar may bring about permanent recovery. Administration of levulose, galactose and maltose may be followed by temporary slight improvement in the symptoms and they cause a marked increase in the blood sugar. Arabinose, xylose, sucrose and lactose have no apparent

TABLE 10.—*Results of the Analyses of the Contents of the Stomach Following the Hypodermic Injection of Insulin and Dextrose in a Dog Provided With a Gastric Fistula*

Dog 3, female, weighing 10.7 Kg.; experiment conducted five days after a gastric fistula was made.

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	74	83	7.8
1/2.....	0.104	95	105	4.0
3/4.....	88	99	4.0
1.....	0.102	60	70	4.0
Following a hypodermic injection of 20 units of insulin				
1/4.....	0.095	45	55	0.3
1/2.....	0.081	16	28	0.6
3/4.....	0.067	49	57	4.0
1.....	0.059	124	130	20.2
1 1/4.....	0.059	129	183	18.6
1 1/2.....	0.050	125	131	15.8
Following a hypodermic injection of 100 cc. of 25 per cent dextrose				
1/4.....	0.061	97	106	6.5
1/2.....	0.081	65	80	0.3
3/4.....	0.113	25	35	0.3
1.....	0.086	0	10	0.3

TABLE 11.—*Results of the Analyses of the Contents of the Stomach Following the Hypodermic Injection of Insulin and Dextrose in a Dog with Both Vagi Severed Directly Above the Diaphragm and Provided with Gastric Fistula*

Dog 4, female, weighing 15.2 Kg.; experiment conducted twenty-seven days after severing vagi and four days after providing gastric fistula.

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	41	83	1.3
1/2.....	40	82	0.9
3/4.....	40	82	1.2
1.....	0.082	40	82	2.6
1 1/4.....	38	78	4.0
1 1/2.....	0.088	32	80	0.7
Following a hypodermic injection of 20 units of insulin				
1/4.....	0.079	34	75	1.5
1/2.....	0.064	34	78	1.6
3/4.....	0.059	36	75	3.0
1.....	0.057	39	78	1.5
1 1/4.....	0.050	34	71	1.0
1 1/2.....	0.050	36	68	1.8
1 3/4.....	0.043	30	54	5.0
2.....	0.041	26	67	1.5
Following a hypodermic injection of 200 cc. of 5.6 per cent dextrose				
1/4.....	0.046	27	71	2.0
1/2.....	0.075	27	64	2.2
3/4.....	0.078	28	64	3.8
1.....	0.079	30	68	3.4

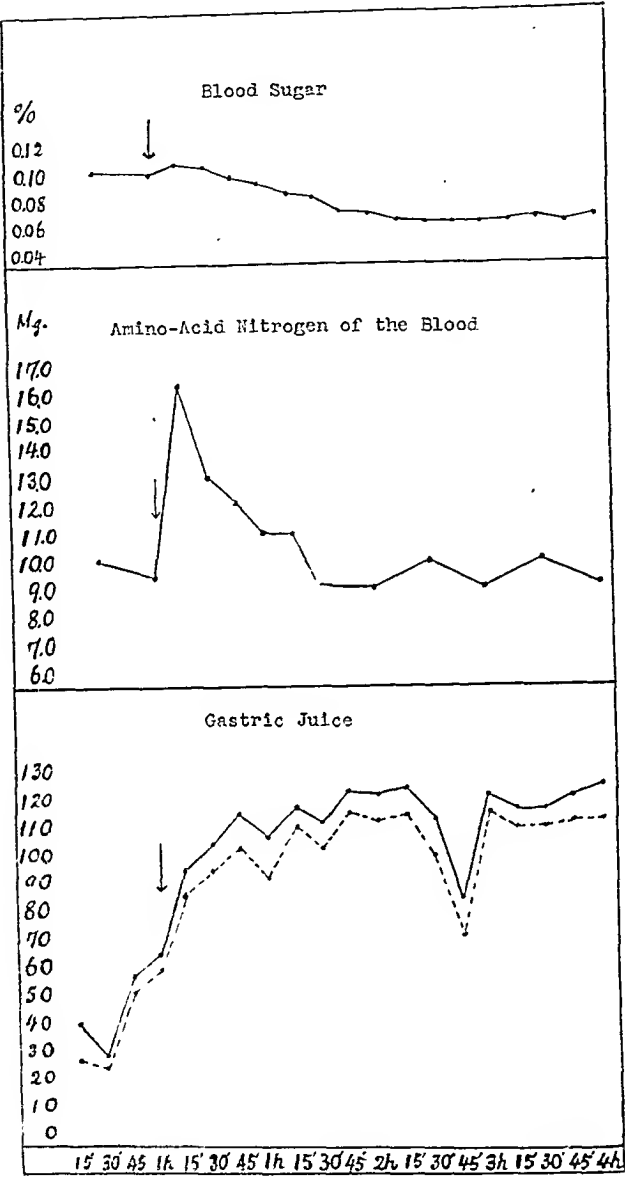


Fig. 2.—The results of analyses of the blood sugar, amino-acid nitrogen of the blood and the gastric juice following an intravenous injection of glycocholate in a man, aged 19 (table 12). A marked increase of the acidity directly after injection may be noted which persists for a long time, while the amino-acid nitrogen content of the blood rapidly resumes the fasting value. The blood sugar curve shows distinct hypoglycemia after a preliminary slight elevation. The arrow indicates the injection of glycocholate. In the curve for gastric juice, in this and the following illustrations, the straight line indicates total acidity and the dotted line free hydrochloric acid.

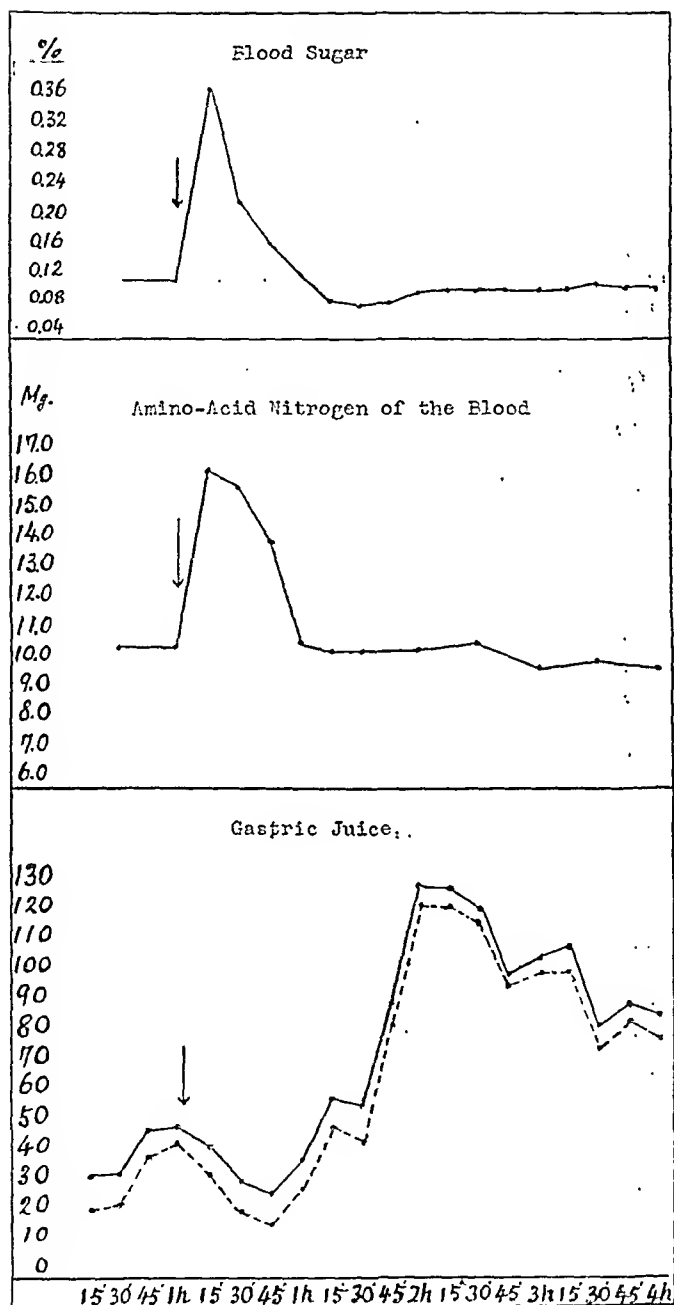


Fig. 3.—The results of analyses of the blood sugar, amino-acid nitrogen of the blood and the gastric juice following an intravenous injection of glycocoll and dextrose in a man, aged 19 (table 14). Following the injection there was suddenly a strong hyperglycemia and an increase of the amino-acid nitrogen content of the blood; the acidity of the gastric juice rather diminished at first and when hyperglycemia was over, increased rapidly. The arrow indicates the injection of glycocoll and dextrose.

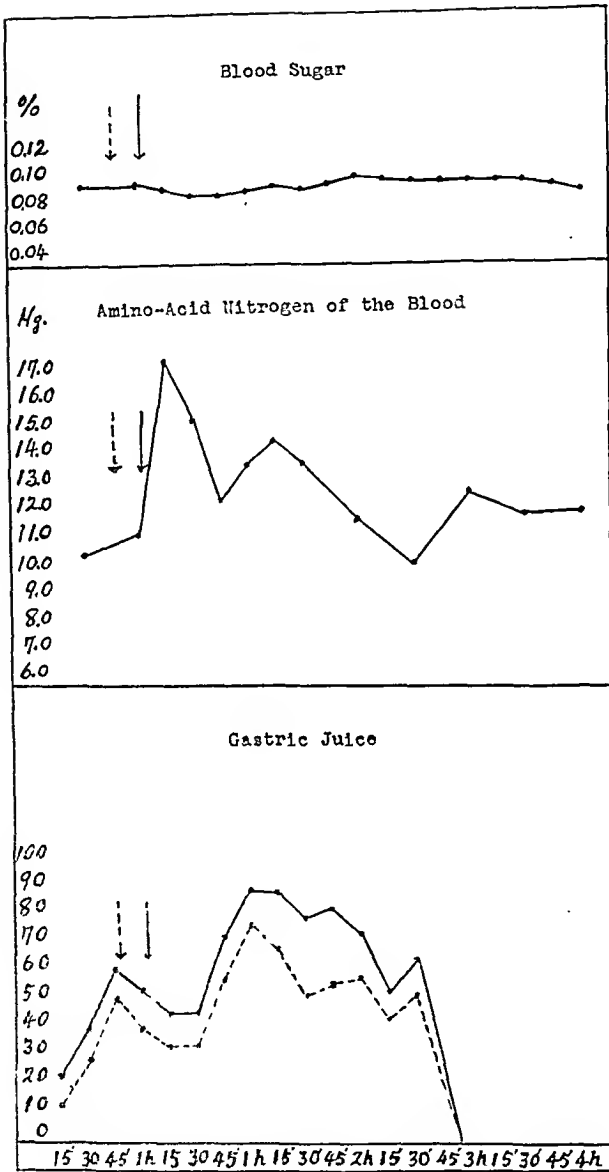


Fig. 4.—The results of the analyses of the blood sugar, amino-acid nitrogen of the blood and the gastric juice following a hypodermic injection of atropine and an intravenous injection of glycocholl in a man, aged 19 (table 15). The acidity of the gastric juice after injection of glycocholl rather diminished at first as a consequence of the inhibitory influence of atropine; the subsequent increase was not so significant as the foregoing curves, and disappeared prematurely. The dotted arrow indicates the injection of atropine, and the straight arrow that of glycocholl.

chose amino-acids, the most important cleavage products of protein, for the investigation of this problem. As the representative of amino-acids, glycocholl and alanine were selected. Glutamic acid and histidine were also used. The amino-acid nitrogen content of the blood was determined by the method of Folin.⁴ Professor Folin supplied us with

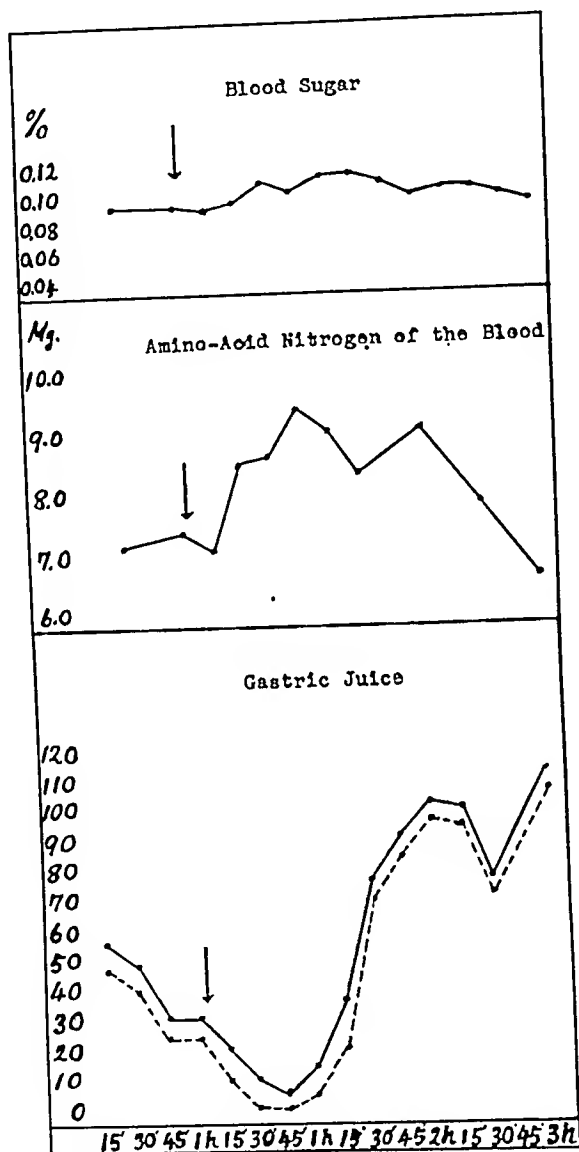


Fig. 5.—The results of analyses of the blood sugar, amino-acid nitrogen of the blood and the gastric juice following an intraduodenal injection of glycocholl in a man, aged 31 (table 16). The glycocholl solution was concentrated so that its resorption was relatively slow; the increase in the acidity of the gastric juice developed later, preceded by a diminution. The arrow indicates the injection of glycocholl.

reagents for this determination and Professor Arai with pure amino-acid preparations.

4. Folin, O., and Wu, H.: A System of Blood Analyses, *J. Biol. Chem.* **38**:81, 1919. Folin, O.: A New Colorimetric Method for the Determination of the Amino-Acid Nitrogen in Blood, *J. Biol. Chem.* **51**:377, 1922.

TABLE 12.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following an Intravenous Injection of 200 Cc. of 5 per Cent Glycocoll in a Man, Aged 19.

Times at Which Speci- mens Were Collected, Hours	Blood Sugar, per Cent	Amino- Acid Nitrogen in Whole Blood, Mg. in 100 Cc.	Gastric Juice			Duodenal Return						
			Free Hydro- chloric Acid	Total Acid- ity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activ- ity)	Amylase Units (Amount × Activ- ity)	Lipase Units (Amount × Activ- ity)	Bile Pigment (Dilu- tion × Amount)	Bile Acids (Dilu- tion × Amount)	
Fasting												
1/4	26	38	30.0							
1/2	0.101	10.01	24	27	5.0	27.0	8,640	35,316	4,185	1,026	54,000	
3/4	50	56	5.5							
1	0.097	9.44	53	64	6.5	26.0	8,320	38,428	2,872	1,170	143,000	
Following an injection of glycocoll												
1/4	0.106	16.21	84	94	29.5							
1/2	0.104	12.89	94	103	17.5	12.0	2,400	20,952	720	288	24,000	
3/4	0.095	12.05	102	114	17.0							
1	0.092	10.85	90	105	31.0	0.8	200	2,051	28	7	360	
1 1/4	0.085	10.85	109	116	26.5							
1 1/2	0.080	9.16	102	110	18.0	15.5	7,750	38,208	1,915	1,705	224,750	
1 3/4	0.069	114	122	35.0							
2	0.067	8.92	111	120	23.5	28.5	14,250	48,279	18,240	4,560	498,750	
2 1/4	0.063	113	123	18.5							
2 1/2	0.060	9.93	98	112	11.0	54.0	27,000	68,094	9,720	5,400	756,000	
2 3/4	0.059	70	83	21.5							
3	0.059	8.92	116	120	15.0	75.0	24,000	83,250	20,625	4,125	900,000	
3 1/4	0.062	108	116	19.5							
3 1/2	0.061	10.09	108	116	32.0	50.0	16,000	47,950	8,000	2,100	525,000	
3 3/4	0.062	112	120	35.5							
4	0.064	9.16	112	124	31.0	18.5	5,920	34,688	2,035	1,073	175,750	

TABLE 13.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following an Intravenous Injection of 200 Cc. of a 5 per Cent Solution of d-Alanine in a Man *

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amino-Acid Nitrogen in Whole Blood, Mg. in 100 Cc.	Gastric Juice			Duodenal Return					
			Free Hydrochloric Acid	Total Acidity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activity)	Amylase Units (Amount × Activity)	Lipase Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting											
¼	60	69	11.0						
½	0.107	9.39	10	19	17.0	16.0	5,120	24,560	4,640	272	11,200
¾	8	18	7.5						
1	0.106	9.03	50	59	1.5	5.0	500	9,295	785	140	8,000
Following an injection of alanine											
¼	0.099	14.89	40	51	2.6						
½	0.094	14.00	59	72	21.0	10.6	8,480	27,942	4,982	435	50,880
¾	0.099	13.41	52	64	13.0						
1	0.100	13.13	49	48	30.0	3.6	2,880	12,175	1,044	209	19,800
1¼	0.099	13.13	67	75	23.0						
1½	0.099	12.40	84	93	8.0	64.0	51,200	139,904	74,240	2,432	550,400
1¾	0.094	86	94	13.6						
2	0.088	11.90	90	98	25.4	99.0	49,500	144,738	62,370	7,326	1,386,000
2¼	0.090	96	104	27.0						
2½	0.090	9.48	96	104	28.2	68.0	34,000	122,535	31,280	2,924	544,000
2¾	0.092	115	123	29.0						
3	0.088	9.39	111	119	25.2	73.0	58,400	159,578	29,200	2,701	584,000
3¼	0.088	107	117	44.5						
3½	0.083	8.57	113	122	23.2	86.0	43,000	159,874	43,860	2,408	584,800
3¾	0.078	112	119	20.0						
4	0.081	9.33	118	129	19.0	90.0	23,800	146,520	32,040	1,620	495,000

* Same man as in table 12.

TABLE 14.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following an Intravenous Injection of 10 Gm. of Glycocoll and 40 Gm. of Dextrose Dissolved in 200 Cc. of Water in a Man *

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amino-Acid Nitrogen in Whole Blood, Mg. in 100 Cc.	Gastric Juice			Duodenal Return					
			Free Hydrochloric Acid	Total Acidity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activ-ity)	Amylase Units (Amount × Activ-ity)	Lipase Units (Amount × Activ-ity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting											
1/4	0.105	10.22	18	29	9.0						
1/2	0.103	10.30	20	30	11.2	29.5	7,375	36,020	7,080		
3/4			36	44	5.3						
1			40	45	17.0	18.5	4,625	32,394	4,070	325	14,750
Following an injection of glycocoll and dextrose											
1/4	0.358	16.10	30	39	10.7						
1/2	0.211	15.52	18	28	4.8	6.5	1,625	14,047	1,723		
3/4	0.151	13.70	13	24	4.3						
1	0.106	10.39	26	35	7.4	2.5	625	6,970	375	475	29,250
1 1/4	0.073	10.03	46	56	5.0						
1 1/2	0.066	10.03	41	53	11.7	6.5	2,600	22,932	975	140	7,500
1 3/4	0.069	10.07	81	87	26.5						
2	0.082	10.07	121	127	17.0	33.5	26,800	91,120	24,120	377	20,150
2 1/4	0.086	10.39	120	126	22.2						
2 1/2	0.084	10.39	116	119	1.5	77.0	38,500	136,598	71,610	9,380	492,450
2 3/4	0.085	9.47	94	97	4.0						
3	0.085	9.47	98	103	11.5	117.0	37,440	151,398	40,950	9,240	754,600
3 1/4	0.087	9.76	98	107	12.3						
3 1/2	0.096	9.76	72	80	6.5	120.0	38,400	156,720	43,920	7,254	468,000
3 3/4	0.091	9.54	82	88	17.5						
4	0.087	9.54	76	84	12.0	117.0	37,440	176,436	39,780	4,914	210,600

* Same man as in table 12.

* Same man as in table 12.

TABLE 15.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following a Hypodermic Injection of 2 mg. of Atropine Sulphate * and an Intravenous Injection of 200 Cc. of 5 per Cent Solution of Glycocoll in a Man †

Injection of 200 Cc. of 5 per Cent Solution of Glycocoll in a Man †

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Amino-Acid Nitrogen in Whole Blood, Mg. in 100 Cc.	Gastric Juice			Duodenal Return					
			Free Hydrochloric Acid	Total Acidity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activity)	Amylase Units (Amount × Activity)	Lipase Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting											
1/4	0.089	10.16	8	19	6.8						
1/2	0.089	10.85	25	36	3.4	7.7	3,080	15,670	462	123	5,390
3/4	0.090		47	58	10.8						
1			36	50	9.8	25.2	12,600	61,236	2,772	353	23,910
Following an injection of glycocoll											
1/4	0.087	17.08	30	42	12.0						
1/2	0.083	14.84	30	43	2.0	2.4	960	4,884	192	17	1,080
3/4	0.082	12.11	54	70	3.0						
1	0.085	13.37	73	86	4.5	1.0	250	1,694	95	8	450
1 1/4	0.089	14.28	62	85	5.0						
1 1/2	0.087	13.37	47	76	4.5	0.8	200	1,270	172	6	640
1 3/4	0.091	11.34	53	79	3.5	1.0	50	956	170	11	800
2	0.096	9.87	40	71	6.0	4.8	1,920	8,947	2,342	278	40,800
2 1/4	0.094	12.46	49	62	2.5	7.2	5,760	18,079	5,760	634	126,000
2 1/2	0.092		0	...	2.0						
2 3/4	0.093		0	...	2.0						
3	0.092		0	...	2.0						
3 1/4	0.092	11.62	0	...	3.0	62.0	31,000	107,012	43,710	3,534	868,000
3 1/2	0.093		0	...	0.0	52.0	16,640	32,240	20,800	2,600	728,000
3 3/4	0.089		0	...							
4	0.085	11.60	0	...							

* Atropine sulphate was injected fifteen minutes before the injection of glycocoll.
† Same man as in table 12.

* Atropine sulphate was injected fifteen minutes before the injection of glycocoll.

† Same man as in table 12.

TABLE 16.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following the Intraduodenal Injection of 20 Gm. of Glycocoll Dissolved in 200 Cc. of Distilled Water in a Man, Aged 31 *

Times at Which Speci- mens Were Collected, Hours	Blood Sugar, per Cent	Amino- Acid Nitrogen in Whole Blood, Mg. in 100 Cc.	Gastric Juice			Duodenal Return					
			Free Hydro- chloric Acid	Total Acid- ity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activ- ity)	Amylase Units (Amount × Activ- ity)	Lipase Units (Amount × Activ- ity)	Bile Pigment (Dilu- tion × Amount)	Bile Acids (Dilu- tion × Amount)
Fasting											
¼	46	55	7.6						
½	0.092	7.15	38	47	4.8	5.6	1,792	13,110	358	269	11,200
¾	23	30	6.0						
1	0.092	7.38	22	31	5.7	2.4	240	5,945	173	79	4,440
Following an injection of glycocoll											
¼	0.090	7.08	9	21	26.5						
½	0.094	8.42	0	10	6.0	27.0	8,640	37,300	8,640	1,161	56,700
¾	0.107	8.53	0	6	4.5						
1	0.101	9.32	4	14	6.2	3.5	1,120	5,625	2,333	214	13,300
1¼	0.112	8.92	20	36	9.0						
1½	0.113	8.23	68	76	22.5	2.0	500	2,902	670	18	1,100
1¾	0.106	83	90	37.0						
2	0.096	8.70	95	101	39.0	16.2	8,100	51,986	4,002	1,490	77,600
2¼	0.101	93	98	31.0						
2½	0.101	7.87	70	76	0.6	21.0	10,500	62,391	17,220	2,205	153,300
2¾	0.096						
3	0.092	6.60	105	112	15.0	40.0	12,800	56,800	24,800	1,520	212,000

* The glycocoll solution was concentrated, so that its resorption was very slow. As a result there usually happens at first a reflex inhibition of the gastric secretion and a reflex discharge of the pancreatic juice and bile.

TABLE 17.—Results of the Analyses of the Contents of the Stomach Following an Intravenous Injection of 100 Cc. of a 5 per Cent Solution of Glycocoll in a Dog Provided with a Gastric Fistula

Dog 2, female, weighing 12 Kg.; experiment conducted twenty days after providing the gastric fistula

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		
		Free HCl	Total Acidity	Amount of Juice, Cc.
Fasting				
1/4.....	0.0
1/2.....	0.089	0	Alkaline	1.2
3/4.....	0	Alkaline	1.3
1.....	0.085	0	Alkaline	1.4
Following an injection of glycocoll				
1/4.....	0.107	67	79	2.0
1/2.....	0.100	87	95	3.2
3/4.....	0.098	101	108	6.4
1.....	0.094	124	130	10.2
1 1/4.....	0.080	86	90	14.6
1 1/2.....	0.085	80	90	4.3
1 3/4.....	0.092	93	100	6.3
2.....	0.094	65	73	25.5
2 1/4.....	0.091	85	94	10.0
2 1/2.....	0.089	15	27	1.4

TABLE 20.—Results of the Analyses of the Contents of the Stomach Following an Intravenous Injection of 100 Cc. of a 1 per Cent Solution of Histidine Hydrochloride

A. Dog 5; experiment conducted thirty days after a gastric fistula was made				B. Dog 4; experiment conducted 100 days after severing both vagi, and seventy-seven days after a gastric fistula was made			
Times at Which Specimens Were Collected. Hours.	Gastric Juice			Times at Which Specimens Were Collected, Hours	Gastric Juice		
	Free Hydrochloric Acid	Total Acidity	Amount of Juice, Cc.		Free Hydrochloric Acid	Total Acidity	Amount of Juice, Cc.
Fasting				Fasting			
1/4	91	121	2.5	1/4	88	120	0.6
1/2	94	114	2.5	1/2	84	114	0.5
3/4	94	112	0.8	3/4	68	100	0.2
1	92	114	0.8	1			0.3
Following an injection of histidine hydrochloride				Following an injection of histidine hydrochloride			
1/4	84	105	5.0	1/4	68	110	0.2
1/2	86	101	2.2	1/2			0.5
3/4	87	104	3.0	3/4	90	120	0.2
1	90	110	13.0	1			0.2
1 1/4	80	105	10.0	1 1/4	0.3
1 1/2	62	91	2.0	1 1/2			0.1

TABLE 21.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following the Intraduodenal Injection of Butter in the Amount of 1 Gm. per Kilogram of Body Weight in a Man, Aged 23, Weighing 47 Kg.

Times at Which Specimens Were Collected. Hours	Blood Sugar, per Cent	Fatty Acids in Whole Blood, 100 Cc.	Gastric Juice			Duodenal Return					
			Free Hydrochloric Acid	Total Acidity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount x Activity)	Amylase Units (Amount x Activity)	Lipase Units (Amount x Activity)	Bile Pigment (Dilution x Amount)	Bile Acids (Dilution x Amount)
Fasting											
1/4	8	16	13.0						
1/2	0.088	0.25	86	94	7.2	26.0	13,000	60,242	9,750	1,378	169,000
3/4	90	100	5.0						
1	0.086	0.26	64	68	4.6	41.5	20,750	86,030	62,250	1,743	228,250
Following an injection of butter											
1/4	0.088	0	6	11.4						
1/2	0.088	0.25	6	14	8.6	46.5	37,200	79,794	124,620	14,880	1,081,500
3/4	0.079	6	14	9.8						
1	0.075	0.25	6	14	9.0	25.0	20,000	42,900	72,500	4,150	850,000
1 1/4	0.076	2	10	7.4						
1 1/2	0.075	0.30	2	10	7.0	25.0	50,000	51,825	112,500	4,950	1,000,000
1 3/4	0.075	10	22	5.0						
2	0.079	0.28	4	12	6.5	18.5	37,000	38,351	70,300	3,700	740,000
2 1/4	0.086	20	25	2.0						
2 1/2	0.086	0.24	4	12	2.5	11.5	11,500	27,198	60,950	2,415	460,000
2 3/4	0.079	0	...	9.8						
3	0.082	0.24	59	67	18.0	30.0	60,000	74,820	114,000	5,760	1,200,000

amino-acids, after entering the circulatory system, stimulate the autonomic nervous center and from this center the stimulus is transmitted through the autonomic nervous system to the reacting tissue cells. The manner in which such substances as amino-acids excite the secretory activity might be called "the humoroneural excitation of the digestive juices" (in this case, "of the gastric juice"). The amino-acids act in just the contrary manner to dextrose. The question whether these amino-acids have also a direct influence on the secretory mechanism of the pancreatic and biliary glands is next considered. Our investigation showed that the secretions of pancreatic juice and bile rather diminish at first (one hour and somewhat longer), followed by a pronounced increase. The results secured by one of us (K. K.) in a dog provided with a pancreatic or biliary fistula coincide with those mentioned. The profuse secretion that is observed later seems to be due mainly to the secretin mechanism and sometimes partly also to hypoglycemia, as at this period the gastric secretion is already profuse and hypoglycemia often occurs. We often observed a reactive hypoglycemia after the administration of amino-acids just as after that of sugar though to a less degree, which was perhaps due to the discharge of insulin into the circulatory system from the pancreas. The duodenal return collected at this period is usually dilute and is rather secretin juice than nervous secretion. From the foregoing facts we conclude that amino-acids excite the gastric secretion humoroneurally, and as a consequence the secretin mechanism develops which causes secondarily the pancreatic and biliary secretions.

The action of fats on the secretory activity of the digestive juices was studied. It is in general accepted that fats are strong excitants of the pancreatic and biliary secretions. The action of fats on the gastric secretion, however, is not invariable. It is generally accepted that fats cause an inhibition of the gastric secretion in the first phase (from 2 to 4 hours), while they cause an increased secretion, with low digesting power, in the second phase lasting for several hours. We used butter and olive oil for intraduodenal administration and a cod liver oil and lecithin preparation for intravenous injection. The determination of lipoids (fat) in the blood was carried out by the method of Bloor.⁵

5. Bloor, W. R.: A Method for Determination of Fat in Small Amounts of Blood, *J. Biol. Chem.* **17**:377, 1914; A Method for the Determination of Lecithin in Small Amounts of Blood, *ibid.* **22**:133, 1915; The Determination of Cholesterol in Blood, *ibid.* **24**:227, 1916. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *ibid.* **52**:191, 1922. Bloor, W. R.: Methods for the Determination of Phosphoric Acid in Small Amounts of Blood, *ibid.* **36**:33, 1918.

TABLE 22.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following the Intraduodenal Injection of 200 Cc. of a 25 per Cent Solution of Dextrose and Butter in the Amount of 1 Gm. per Kilogram of Body Weight in a Man *

Time at Which Speci- mens Were Collected, Hours	Blood Sugar, per Cent	Fatty Acids in Whole Blood, Mg. per 100 Cc.	Gastric Juice			Duodenal Return†					
			Free Hydro- chloric Acid	Total Acid- ity	Amt. of Juice, Cc.	Amt. of Juice, Cc.	Trypsin Units (Amount × Activ- ity)	Amylase Units (Amount × Activ- ity)	Lipase Units (Amount × Activ- ity)	Bile Pigment (Dilu- tion × Amount)	Bile Acids (Dilu- tion × Amount)
Fasting											
1/4	36	44	5.0						
1/2	0.080	0.21	4	12	3.5	22.0	17,600	48,268	6,930	440	44,000
3/4	Alkaline		8.6						
1	0.082	0.25	Alkaline		1.8	38.5	30,800	81,543	18,865	2,888	423,500
Following an injection of dextrose and butter											
1/4	0.155	Alkaline		4.6						
1/2	0.182	0.27	Alkaline		42.0	20.0	10,000	18,420	30,000	2,640	400,000
3/4	0.149	Alkaline		0.0						
1	0.105	0.30	Alkaline		14.0	4.0	3,200	6,656	3,560	36	26,000
1 1/4	0.073	Alkaline		15.2						
1 1/2	0.069	0.27	Alkaline		0.5	10.0	10,000	23,090	39,000	1,000	200,000
1 3/4	0.068	Alkaline		10.0						
2	0.068	0.25	2	14	4.0	37.0	37,000	66,415	123,800	12,580	1,480,000
2 1/4	0.075	18	26	4.0						
2 1/2	0.077	0.24	50	58	5.4	50.0	50,000	99,950	255,000	9,000	2,100,000
2 3/4	0.080	62	70	2.5						
3	0.084	0.25	40	50	4.8	61.0	48,800	97,356	128,100	5,734	976,000

* Same man as in table 20.

† That the duodenal return at one hour is scant notwithstanding the fact that the fatty acids content of the blood is highest at this period shows the inhibitory influence of dextrose.

TABLE 23.—Results of the Analyses of the Contents of the Duodenum Following the Intraduodenal Injection of Butter in the Amount of 1 Gm. per Kilogram of Body Weight and a Hypodermic Injection of 2 mg. of Atropine Sulphate* in a Man †

Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Fatty Acids in Whole Blood, Gm. per 100 Cc.	Duodenal Return					
			Amount of Juice, Cc.	Trypsin Units (Amount × Activity)	Amylase Units (Amount × Activity)	Lipase Units (Amount × Activity)	Bile Pigment (Dilution × Amount)	Bile Acids (Dilution × Amount)
Fasting								
1/4						
1/2	52.0	16,640	72,644	19,032	2,236	416,000
3/4						
1	0.087	0.23	9.5	3,040	13,272	4,275	399	76,000
Following an injection of butter								
1/4	0.091							
1/2	0.096	0.24	25.0	50,000	54,800	13,500	16,250	1,875,000
3/4	0.087							
1	0.091	0.29	1.2	1,200	1,831	2,904	612	45,600
1 1/4	0.084							
1 1/2	0.093	0.28	35.0	17,500	45,150	94,500	7,000	6,125,000
1 3/4	0.090							
2	0.096	0.22	17.0	13,600	24,140	44,880	5,100	3,060,000
2 1/4	0.093							
2 1/2	0.091	0.23	15.5	12,200	24,149	44,020	5,735	232,500
2 3/4	0.087							
3	0.082	0.23	25.0	20,000	40,650	95,000	7,500	425,000

* Atropine sulphate was injected fifteen minutes after the butter. From fifteen to forty-five minutes after the injection no secretion of pancreatic juice and bile occurred, notwithstanding the fact that the fatty acids content of the blood was highest at this period.

† Same man as in table 21.

TABLE 25.—Results of the Analyses of the Contents of the Stomach and the Duodenum Following an Intravenous Injection of 100 Cc. of a Cod Liver Oil and Lecithin Preparation (6 per Cent Fat Emulsion) in a Man, Aged 31

Times at Which Specimens Were Collected, Hours	Gastric Juice					Duodenal Return					
	Fatty Acids in Blood, Gm. per 100 Cc.	Lecithin in Whole Blood, Gm. per 100 Cc.	Cholesterol in Whole Blood, Gm. per 100 Cc.	Total of Free HCl, Amt. of Juice, Amt. of Juice, Cc.			Tryp-sin Units (Rmt. × Activ-ity)	Amy-lase Units (Amt. × Activ-ity)	Lipase Units (Amt. × Activ-ity)	Bile Pig-ment (Dilu-tion × Activ-ity)	Bile Acids (Dilu-tion × Activ-ity)
	Sugar, per Cent	Whole Blood, Gm. per 100 Cc.	Whole Blood, Gm. per 100 Cc.	Free HCl	Amt. of Juice, Cc.	Amt. of Juice, Cc.					
Fasting											
1/4	4	12	20.0					
1/2	0.093	0.234	0.253	2	11	7.0	1.8	360	3,866	108	7
3/4	8	18	4.0					540
1	0.094	0.236	0.254	6	14	1.2	1.2	120	2,092	74	4
											300
Following an injection of cod liver oil and lecithin preparation											
1/4	0.094	0.0					
1/2	0.085	0.259	0.288	0.0	7.0	9,400	19,237	4,550	406
3/4	0.080	2	14	11.5					15,400
1	0.076	0.250	0.263	4	18	4.8	14.3	18,376	42,342	7,150	2,517
1 1/4	0.076	29	36	50.0					121,550
1 1/2	0.076	0.242	0.255	30	37	6.0	10.0	12,500	29,940	8,200	4,200
1 3/4	0.073	21	29	16.0					100,000
2	0.076	0.236	0.253	11	18	3.0	14.3	11,360	42,969	15,620	6,840
2 1/4	0.075	0	8	3.0					85,200
2 1/2	0.080	0.231	0.260	19	28	9.0	10.8	8,640	20,650	3,456	1,026
2 3/4	0.080	18	29	6.0					45,360
3	0.085	0.235	0.257	0	11	5.0	2.5	2,000	6,808	1,250	395
											13,750

TABLE 26.—Results of the Analyses of the Gastric Juice of a Man, Aged 24: A, Following the Intraduodenal Injection of 200 Cc. of 25 per Cent Dextrose, and the Administration by Mouth of 200 Cc. of a 5 per Cent Solution of Meat Extract; B, Following the Intraduodenal Injection of 200 Cc. of Distilled Water and the Administration by Mouth of 200 Cc. of a 5 per Cent Solution of Meat Extract *

A			B		
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice: Free Hydro-chloric Acid	Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice: Free Hydro-chloric Acid
Fasting					
1/4	76	1/4	42
1/2	0.092	84	1/2	0.118	51
3/4	82	3/4	52
1	0.088	78	1	0.124	20
Following an injection of dextrose			Following an injection of distilled water		
1/4	0.138	10	1/4	0.131	27
1/2	0.165	4	1/2	0.105	29
Following the administration of meat extract			Following the administration of meat extract		
1/4	0.134	0	1/4	0.102	0
1/2	0.113	0	1/2	0.085	46
3/4	0.104	0	3/4	0.092	64
1	0.086	0	1	0.092	69
1 1/4	0.083	0	1 1/4	0.105	58
1 1/2	0.091	4	1 1/2	0.099	30
1 3/4	0.101	48			
2	0.107	72			
2 1/4	0.101	86			
2 1/2	0.104	64			

* The gastric secretion is inhibited for about one hour when dextrose was injected, in comparison with the results of the controlling research. The remnants of meat extract were found in the former for about two hours, while in the latter for about one hour, showing that the gastric motility was also perceptibly inhibited when dextrose was injected. This inhibition develops also when an isotonic solution of dextrose is used if the amount of it is sufficient.

TABLE 28.—Results of the Analyses of the Gastric Juice of a Man, Aged 23; A, Following the Intraduodenal Injection of 200 Cc. of a 25 per Cent Solution of Dextrose and the Administration by Mouth of 300 Cc. of a 5 per Cent Alcohol; B, Following the Intraduodenal Injection of 200 Cc. of Distilled Water and the Administration by Mouth of 300 Cc. of 5 per Cent Alcohol

A				B			
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice	
		Free* Hydrochloric Acid	Total Acidity			Free Hydrochloric Acid	Total Acidity
Fasting				Fasting			
$\frac{1}{4}$	53	62	$\frac{1}{4}$	51	60
$\frac{1}{2}$	0.090	38	48	$\frac{1}{2}$	0.081	60	63
$\frac{3}{4}$	88	98	$\frac{3}{4}$	55	64
1	0.092	60	72	1	0.076	64	71
Following an injection of dextrose				Following an injection of distilled water			
$\frac{1}{4}$	0.149	40	50	$\frac{1}{4}$	0.072	31	40
$\frac{1}{2}$	0.194	0	4	$\frac{1}{2}$	0.074	32	44
Following the administration of alcohol				Following the administration of alcohol			
$\frac{1}{4}$	0.163	0	2	$\frac{1}{4}$	0.083	9	18
$\frac{1}{2}$	0.133	0	2	$\frac{1}{2}$	0.065	40	47
$\frac{3}{4}$	0.108	0	5	$\frac{3}{4}$	0.065	32	38
1	0.087	0	7	1	0.087	37	43
$1\frac{1}{4}$	0.094	0	6	$1\frac{1}{4}$	0.078	56	65
$1\frac{1}{2}$	0.097	11	17	$1\frac{1}{2}$	0.081	78	87
$1\frac{3}{4}$	0.094	43	54	$1\frac{3}{4}$	0.078	62	71
2	0.092	69	77	2	0.081	60	67
$2\frac{1}{4}$	0.090	67	74	$2\frac{1}{4}$	0.083	43	50
$2\frac{1}{2}$	0.085	70	79	$2\frac{1}{2}$	0.085	28	36
$2\frac{3}{4}$	0.087	102	114	$2\frac{3}{4}$	0.081	43	53
3	0.085	68	78	3	0.078	33	43

* The appearance of the free hydrochloric acid was retarded for one hour and fifteen minutes in the main research.

TABLE 29.—Results of the Analyses of the Gastric Juice of a Man, Aged 23; A, Following the Intraduodenal Injection of 200 Cc. of a 25 per Cent Solution of Dextrose and the Administration by Mouth of 0.2 Gm. of Caffeine Dissolved in 300 Cc. of Distilled Water; B, Following the Intraduodenal Injection of 200 Cc. of Distilled Water and the Administration by Mouth of 0.2 Gm. of Caffeine Dissolved in 300 Cc. of Distilled Water

A				B			
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice	
		Free* Hydrochloric Acid	Total Acidity			Free Hydrochloric Acid	Total Acidity
Fasting				Fasting			
$\frac{1}{4}$	46	58	$\frac{1}{4}$	20	29
$\frac{1}{2}$	0.072	24	37	$\frac{1}{2}$	0.081	10	20
$\frac{3}{4}$	50	65	$\frac{3}{4}$	24	30
1	0.076	90	100	1	0.076	32	40
Following an injection of dextrose				Following an injection of distilled water			
$\frac{1}{4}$	0.160	58	63	$\frac{1}{4}$	0.065	6	18
$\frac{1}{2}$	0.191	30	40	$\frac{1}{2}$	0.062	10	20
Following the administration of caffeine				Following the administration of caffeine			
$\frac{1}{4}$	0.170	0	3	$\frac{1}{4}$	0.072	0	4
$\frac{1}{2}$	0.143	0	2	$\frac{1}{2}$	0.076	0	15
$\frac{3}{4}$	0.133	0	2	$\frac{3}{4}$	0.072	26	34
1	0.092	0	2	1	0.074	36	46
$1\frac{1}{4}$	0.072	0	2	$1\frac{1}{4}$	0.078	77	84
$1\frac{1}{2}$	0.074	12	25	$1\frac{1}{2}$	0.076	61	70
$1\frac{3}{4}$	0.072	79	90	$1\frac{3}{4}$	0.078	66	74
2	0.076	110	119	2	0.081	67	75
$2\frac{1}{4}$	0.074	116	124				
$2\frac{1}{2}$	0.076	128	136				
$2\frac{3}{4}$	0.076	125	135				
3	0.078	37	45				

* The appearance of the free hydrochloric acid was retarded one hour in the main research.

TABLE 30.—Results of the Analyses of the Gastric Juice of a Man, Aged 34; A, Following the Repeated Intraduodenal Injection of a 25 per Cent Solution of Dextrose and the Administration by Mouth of a Test Breakfast (Bread 35 Gm., and Water 300 Cc.); B, Following the Repeated Intraduodenal Injection of Distilled Water and the Administration by Mouth of a Test Breakfast

1. Administration by Mouth of a Test Breakfast

Times at Which Specimens Were Collected, Hours	A			B		
	Blood Sugar, per Cent	Gastric Juice		Blood Sugar, per Cent	Gastric Juice	
		Free Hydrochloric Acid	Total Acidity		Free Hydrochloric Acid	Total Acidity
Fasting	30	37	Fasting	36
1/4	0.079	30	41	1/4	0.101	43
1/2	39	47	1/2	70
3/4	0.095	36	45	3/4	0.099	69
1				1		
Following an injection of 200 cc. of dextrose				Following an injection of 200 cc. of distilled water		
1/4	0.117	20	26	1/4	0.103	48
1/2	0.185	14	20	1/2	0.101	50
Following the administration of a test breakfast				Following the administration of a test breakfast		
1/4	0.201	0	2	1/4	0.098	27
1/2	0.173	0	2	1/2	0.104	46
3/4	0.133	0	9	3/4	0.107	67
Following the injection of 200 cc. of dextrose				Following the injection of 200 cc. of distilled water		
1	0.140	0	12	1	0.105	76
1 1/4	0.119	0	12	1 1/4	0.109	75
1 1/2	0.107	0	13	1 1/2	0.101	70
1 3/4	0.117	0	11	1 3/4	0.097	72
2	0.109	0	12	2	0.099	57
2 1/4	0.101	0	13	2 1/4	0.093	27
2 1/2	0.089	0	52	2 1/2	0.096	
2 3/4	0.093	40	59			
3	0.097	45				

No juice

TABLE 31.—Results of the Analyses of the Gastric Juice of a Man, Aged 33; A, Following the Repeated Intraduodenal Injection of a 25 per Cent Solution of Dextrose and the Administration by Mouth of 300 Cc. of 5 per Cent Alcohol; B, Following the Repeated Intraduodenal Injection of Distilled Water and the Administration by Mouth of 300 Cc. of 5 per Cent Alcohol

Administration by Mouth of 300 Cc. of 5 per Cent Alcohol

A				B			
Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice		Times at Which Specimens Were Collected, Hours	Blood Sugar, per Cent	Gastric Juice	
		Free Hydrochloric Acid	Total Acidity			Free Hydrochloric Acid	Total Acidity
Fasting	13	22	Fasting	8	16
1/4	0.109	46	55	1/4	0.098	11	19
1/2	55	64	1/2	12	21
3/4	0.111	62	68	3/4	0.097	12	20
1	0.127	44	54	1	0.100	5	10
Following the injection of 200 cc. of dextrose	0.184	12	24	Following the injection of 200 cc. of distilled water	0.100	24	30
1/4	0.204	0	3	1/4	0.099	10	18
1/2	0.179	0	2	1/2	0.100	14	16
3/4	0.139	0	2	3/4	0.096	14	18
1	0.177	0	2	1	0.098	22	25
Following the injection of 100 cc. of dextrose	0.153	0	2	Following the injection of 100 cc. of distilled water	0.102	26	32
1 1/4	0.141	0	2	1 1/4	0.102	30	33
1 1/2	0.123	0	2	1 1/2	0.096	29	31
1 3/4	0.109	0	2	1 3/4	0.102	20	25
2	0.104	0	2	2	0.103	17	20
2 1/4	0.088	0	2	2 1/4	0.100	3	24
2 1/2	0.081	0	2	2 1/2	0.098	0	18
2 3/4	0.090	0	2	2 3/4	0.089	0	12
3	0.111	0	2	3		0	10
3 1/4	0.102	2	9				
3 1/2	0.100	4	14				
3 3/4	0.097	10	24				

* The subject was drunk from thirty minutes to one hour at the most; after two hours he had almost recovered.

* The subject was drunk from thirty minutes to one hour at the most; after two hours he had almost recovered.

rice-bran extract was used and earliest when alcohol solution was administered. The time at which the hydrochloric acid reappeared, when a previous injection of dextrose was given, was usually one hour and thirty minutes after the ingestion of the test meal, i. e., two hours

TABLE 32.—*Results of the Analyses of the Gastric Juice of a Man, Aged 31; A, Following the Repeated Intraduodenal Injection of 20 per Cent Dextrose and the Administration by Mouth of 300 Cc. of a 5 per Cent Solution of Meat Extract; B, Following the Repeated Intraduodenal Injection of Distilled Water and the Administration by Mouth of 300 Cc. of a 5 per Cent Solution of Meat Extract**

A			B		
Times at Which Specimens Were Collected, Hours Fasting	Blood Sugar, per Cent	Gastric Juice: Free Hydrochloric Acid	Times at Which Specimens Were Collected, Hours Fasting	Blood Sugar, per Cent	Gastric Juice: Free Hydrochloric Acid
$\frac{1}{4}$	24	$\frac{1}{4}$	28
$\frac{1}{2}$	0.083	20	$\frac{1}{2}$	0.082	26
$\frac{3}{4}$	26	$\frac{3}{4}$	34
1	0.085	40	1	0.084	51
Following the injection of 200 cc. of dextrose			Following the injection of 200 cc. of distilled water		
$\frac{1}{4}$	0.156	38	$\frac{1}{4}$	0.085	32
$\frac{1}{2}$	0.189	No juice	$\frac{1}{2}$	0.087	31
Following the administration of meat extract			Following the administration of meat extract		
$\frac{1}{4}$	0.202	0	$\frac{1}{4}$	0.089	0
$\frac{1}{2}$	0.173	0	$\frac{1}{2}$	0.087	0
$\frac{3}{4}$	0.146	0	$\frac{3}{4}$	0.094	22
Following the injection of 100 cc. of dextrose			Following the injection of 100 cc. of distilled water		
1	0.139	0	1	0.087	49
$1\frac{1}{4}$	0.137	0	$1\frac{1}{4}$	0.093	67
$1\frac{1}{2}$	0.075	0	$1\frac{1}{2}$	0.089	64
Following the injection of 100 cc. of dextrose			Following the injection of 100 cc. of distilled water		
$1\frac{3}{4}$	0	$1\frac{3}{4}$	0.075	76
2	0.132	0	2	0.084	80
$2\frac{1}{4}$	0.076	0	$2\frac{1}{4}$	0.085	84
Following the injection of 100 cc. of dextrose			Following the injection of 100 cc. of distilled water		
$2\frac{1}{2}$	0.112	0	$2\frac{1}{2}$	0.072	86
$2\frac{3}{4}$	0.119	0	$2\frac{3}{4}$	0.094	74
3	0.112	0	3	0.087	60
Following the injection of 100 cc. of dextrose			Following the injection of 100 cc. of distilled water		
$3\frac{1}{4}$	0.108	0	$3\frac{1}{4}$	0.084	46
$\frac{1}{2}$	0.138	0	$3\frac{1}{2}$	0.078	33
$3\frac{3}{4}$	0.135	0	$3\frac{3}{4}$	0.085	44
4	0.089	0	4	0.078	16
$4\frac{1}{4}$	0.068	29			
$4\frac{1}{2}$	0.071	36			

* The color of the meat extract was perceivable until the last specimen in main experiment, while the gastric juice was almost colorless after two hours in the control experiment. Gastric motility was also remarkably inhibited in the main experiment.

after the injection of dextrose. From this fact it seems likely that the reappearance of the free hydrochloric acid, when a previous injection of dextrose is made, does not depend on the substances ingested, but on the effect of dextrose itself. To prove this fact more precisely we tried to discover whether the excitatory effect of the substances men-

tioned may be inhibited as long as desired, by repeated injections of dextrose at adequate intervals.

The results of the experiments regarding the influence of repeated injections of dextrose into the duodenum on the excitatory function of the test breakfast, alcohol and meat extract showed that the secretory activity is likely to be inhibited as long as is desired. After repeated injections of dextrose, we observed a complete cessation of the gastric secretion (especially the free hydrochloric acid) for four hours, and it is likely that this cessation might be prolonged much longer if the repetition of injections of dextrose were continued.

COMMENT

That the secretory mechanism of the salivary glands is entirely nervous has been emphatically proclaimed by prominent physiologists. Starling expressed the opinion that "in the mouth the reaction must be rapid, and is entirely nervous." Our results also showed that for this secretion no humoroneural mechanism exists.

The secretion of the intestinal juice is of a special character. The local irritation of the mucous membrane of the intestine, mechanical or chemical, seems the strongest stimulation for this secretion. No direct connection exists between this secretion and the digestive process. If no cannula is inserted into the Thiry-Vella fistula, the secretion is usually minimal or almost stops. When a cannula is inserted into the fistula, the secretion occurs and continues for a long time, regardless of whether the animal is hungry or fed. Consequently, by giving foods (meat, bread, milk) it is impossible to produce a curve that is similar to the one obtained for gastric, pancreatic and biliary secretions. It is therefore logical to assume that the humoroneural regulatory mechanism fails in this viscus.

The sugar that causes an inhibitory influence on the secretory centrum of the digestive juices must be ready for use in the physiologic process of oxidation; on this process the quantity of glycogen stored has little influence. The regulatory influence of this active sugar on the function of the digestive tissues is similar to that of oxygen on the function of the respiratory organs. A deficiency of oxygen stimulates the autonomic nervous centrum; from this centrum the stimulus is transmitted to the respiratory organs and causes a forced respiration. An excess of oxygen provokes an inhibitory stimulus which leads to apnea. As is well known, the incessant oxidation of sugar is unconditionally necessary to maintain the living process. Therefore it is reasonable to suppose a similarity exists between the regulatory mechanism of these two substances and the organs from which they are derived.

Amino-acids stimulate the autonomic nervous center and humoro-neurally provoke the gastric secretion. As a consequence, the secretin mechanism develops and the secretion of pancreatic juice and bile occurs. When protein is ingested, therefore, there is the nervous secretion of the gastric juice and digestion progresses; then, after resorption of the cleavage products of protein, the humoroneural stimulation of the secretory nerve occurs which renders the secretory process more active. The secretin mechanism follows this gastric activity, so that the digestion of protein progresses satisfactorily.

Fats stimulate the autonomic nervous centrum, but mainly that of pancreatic and biliary secretions though that of gastric secretion is not excluded. In other words, amino-acids and fats stimulate the autonomic nervous center: the former, the centrum that controls the gastric secretion, and the latter, mainly the centrum that controls the pancreatic and biliary secretions. Such substances might be called "the humoroneural excitants of the secretions of digestive juices." Dextrose, on the contrary, is "the humoroneural inhibitant." When a mixed diet is ingested in large quantity these excitatory and inhibitory processes must inhibit each other.

The secretory mechanisms of the digestive juices are rather complex, but may be classified as follows:

<i>Secretion</i>	<i>Mechanism</i>
Salivary.....	Neural
Gastric	{ Neural Humoroneural Humoral
Pancreatic	
Biliary	

The neural as well as the humoroneural mechanism is manifested in two opposite directions, namely, excitatory and inhibitory.

As mentioned, the salivary secretion occurs exclusively through the nervous mechanism. It is well known since the painstaking works of Pavlov ⁶ that this mechanism is manifested as the conditional and unconditional reflexes, whereas for the gastric secretion the neural and the humoroneural mechanisms seem to be especially important. The conditional and unconditional reflexes play an important rôle in the neural mechanism when foods are ingested. The humoroneural mechanism, however, must not be neglected at this period. The neural and the humoroneural mechanisms are intimately related. When a digestive hyperglycemia exists, this causes humoroneurally an inhibition of the gastric secretion, so that at this period the neural mechanism may be

6. Pavlov, J. P.: Die höchste Nerventätigkeit (das Verhalten) von Tieren: Eine zwanzigjährige Prüfung der objektiven Forschung Bedingte Reflexe, ed. 3, Munich, J. F. Bergmann, 1926; Les réflexes conditionnels: Etude objective de l'activité nerveuse supérieure des animaux, Paris, Félix Alcan, 1927.

SUMMARY

1. The salivary secretion is entirely nervous. No humoroneural mechanism for this secretion exists.

2. The secretion of the intestinal juice is of special character, and the humoroneural regulatory mechanism fails in this viscus.

3. The sugar that causes an inhibitory influence on the secretory center of the gastric, pancreatic and biliary juices must be ready for use in the physiologic process of oxidation. The quantity of glycogen stored has little influence on this process.

4. Amino-acids stimulate the autonomic nervous center and humoroneurally provoke the gastric secretion ("the humoroneural excitant of the gastric secretion"). As a consequence the secretin mechanism develops, and there is profuse secretion of pancreatic juice and bile.

5. Fats also stimulate the autonomic nervous centrum, mainly that of pancreatic and biliary secretions, though that of gastric secretion is not excluded ("the humoroneural excitant of the secretion of digestive juices").

6. The secretory mechanisms of the digestive juices are rather complex, but may be classified as follows:

Secretion

Salivary.....	Neural
Gastric	$\left\{ \begin{array}{l} \text{Neural} \\ \text{Humoroneural} \\ \text{Humoral} \end{array} \right.$
Pancreatic	
Biliary	

The neural, as well as the humoroneural, mechanism is manifested in two opposite directions, namely excitatory and inhibitory.

7. The gastric secretion is subjected mainly to the neural and humoroneural mechanisms, while the humoral mechanism plays a lesser rôle.

8. The secretory activity of pancreatic juice and bile follows mainly the humoral and the humoroneural mechanisms, while the neural mechanism seems to play a lesser rôle than in the upper part of the digestive tracts. When the gastric secretion is disturbed, however, the humoroneural mechanism plays the main rôle, associated with the neural mechanism.

9. When both vagi are severed directly above the diaphragm, the humoroneural regulatory mechanism disappears, so that the importance of the autonomic nervous center and the vagus nerve for this mechanism is conclusively proved.

10. The hyperglycemia caused by the intraduodenal administration of dextrose thoroughly inhibits the secretory activity of the stomach when a series of test meals are ingested and it is possible to continue

this inhibitory impulse as long as is desired by repeated injections of dextrose. This fact shows that hyperglycemia inhibits not only the first phase of the gastric secretion but also the second phase, so far as this is provoked by humoroneural excitants.⁷

7. In the first paper of this series (Arch. Int. Med. **42**:216 [Aug.] 1928), p. 273, lines 21 and 22, "The last tube in the row in which turbidity appears," should read "The last tube in the row in which no turbidity appears; in the third paper (ibid. **43**:413 [March] 1929), p. 416, line 17, "case 2" should read "case 11"; in the fourth paper (ibid. **43**:446 [April] 1929), p. 451 to 463, in table 1 to table 15, "Kilo-Units" should be "Units"; on p. 465 of the same paper the figures in the last two columns should be transposed.

THE EFFECT OF CARDIAC RATE AND THE INHALATION OF OXYGEN ON TRANSIENT BUNDLE BRANCH BLOCK *

BENJAMIN M. BAKER, JR., M.D.

BALTIMORE

While temporary or recurring abnormalities of supraventricular conduction are common, notably during the administration of digitalis or during the course of rheumatic fever, disturbances of intraventricular conduction are more often permanent. Deranged right or left bundle conduction in clinical cases has been recognized since the experimental demonstration by Eppinger and Rothberger¹ of the form of galvanometric curves obtained by sectioning the bundle in dogs. A number of anatomic studies has resulted in the demonstration of lesions affecting one or the other bundle in hearts from which, during life, curves had been recorded characteristic of bundle branch block. Evidence of this type of inefficiency of the conducting system is usually observed to persist, but to this generalization there are conspicuous exceptions. Lewis,² Mathewson,³ Carter^{3a} and Robinson⁴ each published records showing transient bundle branch block as a temporary phenomenon.

It is the purpose of this communication to record further observations on temporary bundle branch block and to discuss the nature of transient disturbances in the conduction of the excitatory process within the ventricular specialized tissue.

* Submitted for publication, Nov. 15, 1929.

* From the Cardiographic Laboratory of the Johns Hopkins Hospital and University.

1. Eppinger and Rothberger: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, *Ztschr. f. klin. Med.* **70**:1, 1910.

2. Lewis: Certain Physical Signs of Myocardial Involvement, *Brit. M. J.* **1**:484 (March 8) 1913.

3. Mathewson: Lesions of the Branches of the Auriculo-Ventricular Bundle, *Heart* **4**:385, 1912-1913.

3a. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, *Arch. Int. Med.* **13**:803 (May) 1914.

4. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch. Int. Med.* **18**:830 (Dec.) 1916. Robinson, G. C.: The Significance of Abnormalities in the Form of the Electrocardiogram, *Arch. Int. Med.* **24**:422 (Oct.) 1919.

The thorax was large with horizontal ribs; there was symmetrical limitation of respiratory excursions. The anteroposterior diameter was increased. No abnormalities were noted on percussion or auscultation save for the signs of well marked emphysema. No râles were heard at the bases.

No shock, thrill or bulge was noted. There were no localized pulsations. The point of maximum impulse was not seen but barely felt in the fifth interspace, 11 cm. to the left of the midsternal line. Percussion outlines in the intercostal areas indicated dullness to the right and left of the sternum as follows:

3 cm.	II	3.5 cm.
	III	5.5 cm.
3 cm.	IV	8 cm.
	V	11.5 cm.

Sounds of moderate intensity were heard. The first systolic sound at the apex was sharp and not reduplicated, followed by a short, soft, low pitched systolic

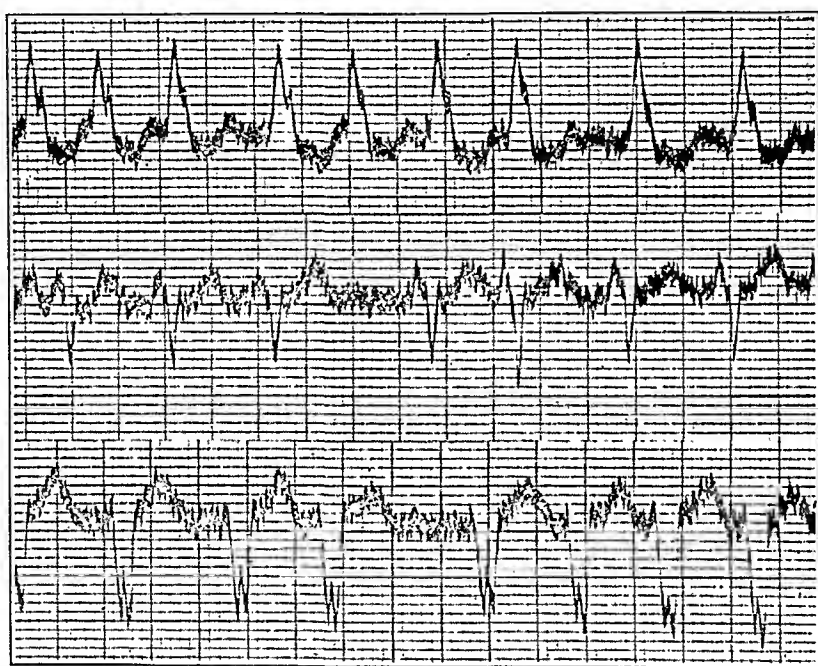


Fig. 1.—Curve recorded Jan. 9, 1929, showing no regularly spaced P waves; marked notching of R I and III with slurring of R I; T waves opposite to main ventricular deflection in all leads; QRS 0.11 seconds. The levocardiogram was predominant. Auricular fibrillation is shown with right bundle branch block. The rate was approximately 142.

murmur, not transmitted to the axilla nor over the body of the heart. No diastolic murmur was heard. The sound was less distinct over the base of the heart. In the second right interspace the first systolic sound was barely heard and was followed by a short, soft, high pitched murmur occupying the first half of systole. The second systolic sound was not loud but was distinctly tympanic and was easily heard over the vessels of the neck.

At times the cardiac rhythm was regular. After moderate exercise, the rhythm became grossly irregular. No alteration could be detected in the quality of the

heart sounds during the periods of irregularity save that they were definitely of softer tone.

The pulse rate was slow, and while the patient was at rest it was regular and of good volume. The tension was apparently increased. The vessel walls were greatly thickened and tortuous.

There was no tenderness or rigidity of the abdomen. No masses were visible or palpable. There was a flat sound on percussion over the liver from the fifth interspace to the costal margin in the midclavicular line. There was no tenderness in the right upper quadrant. The spleen was not palpable; there was no evidence of fluid in the peritoneal cavity.

There was no clubbing of the fingers, no weakness, atrophy or trophic disturbances and no edema.

Neurologic examination gave negative results.

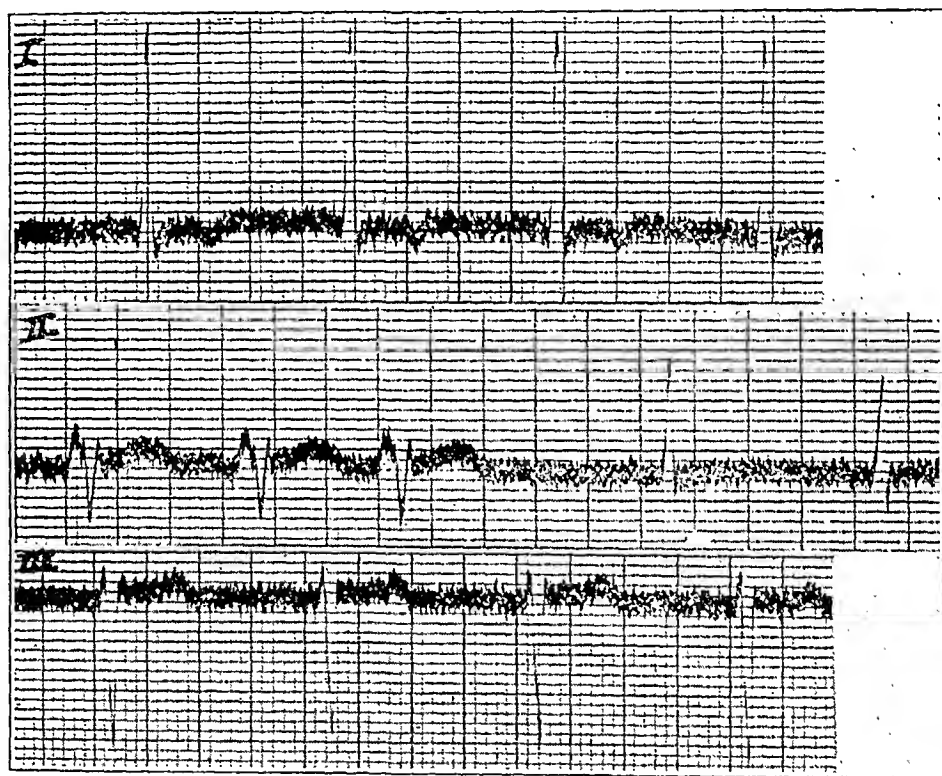


Fig. 2.—Record taken Jan. 18, 1929, while patient was ambulatory. The rate during normal intraventricular conduction was 78. Regularly spaced P waves are occasionally visible; sino-auricular rhythm; P-R interval, 0.15 seconds; QRS, 0.05 seconds. The main ventricular deflections are upward. The first three complexes of lead II are conspicuously different. The ventricular deflections are downward. The rate was 92. The curve shows slurring of R waves; delay in intraventricular conduction. The levocardiogram was predominant.

Laboratory Studies.—The hemoglobin was 90 per cent; the red blood cells numbered 4,100,000 per cubic millimeter and the white blood cells, 7,250 per cubic millimeter. Differential formula and smear were normal.

The urine was clear and bright yellow. The following observations were noted: specific gravity, 1.015; acid; sugar, 0; albumin, faint trace throughout hospital

admission. Microscopic examination showed occasional hyaline and finely granular casts, but no leukocytes and no red blood cells were found.

The Wassermann reaction was negative in both icebox and water bath fixations.

Teleoroentgenogram: M. R., 4 cm.; M. L., 10.5 cm. The transverse diameter of the chest was 30 cm.

The excretion of phenolsulphonphthalein was 45 per cent in two hours.

The specific gravity varied from 1.013 to 1.022. The volume of urine during the day was 565 cc. and during the night, 325 cc.

The nonprotein nitrogen was 37 mg. per cent. The blood sugar during fasting was 104 mg. per cent. The vital capacity was 2.6 liters or 70 per cent of normal for the patient's weight and occupation.

DISCUSSION OF ILLUSTRATIONS

All records were made with the customary three leads and standardized so that a passage of 1 millivolt through the string resulted in a deflection of 1 cm. on the camera scale.

The curve shown in figure 1, recorded Jan. 9, 1929, when the patient was first observed, reveals complexes characteristic of auricular fibrillation and intraventricular block of the right bundle branch type. In the second record (fig. 2) taken nine days later, a conspicuous change is to be noted. The normal sinus rhythm with normal ventricular complexes in lead I changes to three aberrant ventricular complexes in lead II, followed by normal auricular waves and normal intraventricular conduction.

Figure 3 shows persistent auricular fibrillation; there the normal ventricular complexes give way to characteristic aberrant complexes as the ventricular rate becomes more rapid.

Following rest in bed and the administration of 2.9 Gm. of powdered digitalis leaves for a period of twenty-five days, the first strip of figure 4 was obtained, showing normal sinus rhythm with normal intraventricular conduction. The patient was then made to raise and lower the right leg rapidly, and five minutes later the second strip of figure 4 was obtained showing an increase in cardiac rate from 58 to 91. With this more rapid rate, aberrant ventricular complexes replaced the previously normal ones. In figure 5 the actual transition, induced by exercise, is recorded.

Figure 6 shows the effects of the administration of oxygen for five minutes, by means of a mask, followed by exercise. Contrary to the effects of exercise in figures 4 and 5, following the inhalation of oxygen, exercise increased the cardiac rate without bringing about disturbed conduction through the ventricular conducting system.

This observation was confirmed in figure 7, in which it can also be seen that the administration of oxygen brought about the disappearance of evidence of impaired intraventricular conduction.

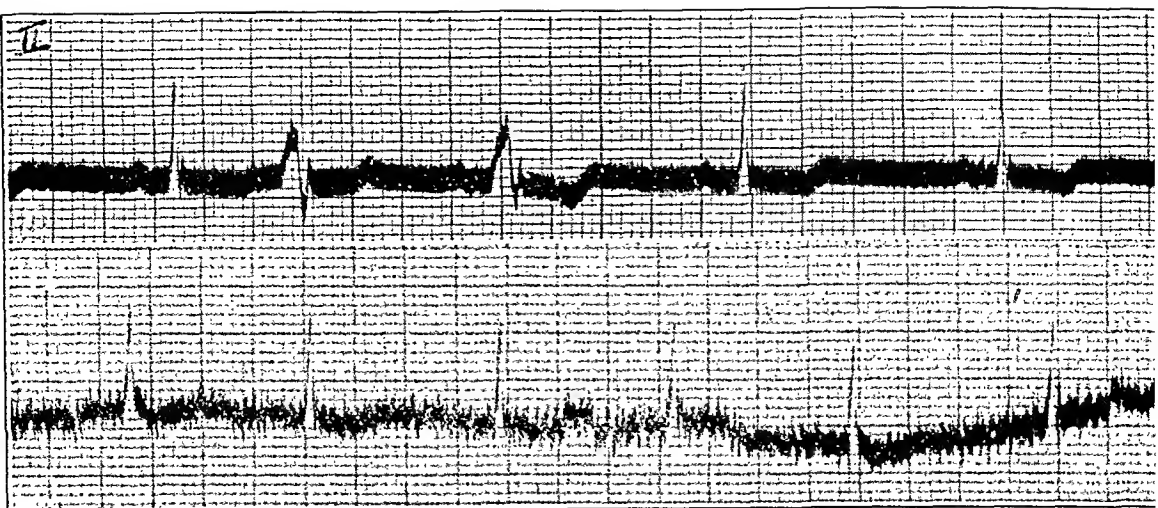


Fig. 6.—Record taken Feb. 27, 1929. The upper curve shows normal sinus rhythm throughout and normal and aberrant ventricular complexes. The rate was 74. The R-R interval between the second and third complexes was 0.84 seconds and between the third and fourth complexes, 0.95 seconds. In the first two instances aberrant ventricular complexes occur and in the fourth a normal complex. The lower curve was obtained following the inhalation of oxygen for five minutes and during exercise of the right leg. The rate was 90; the average "R-R" interval, 0.67 seconds. Ventricular complexes were all normal.

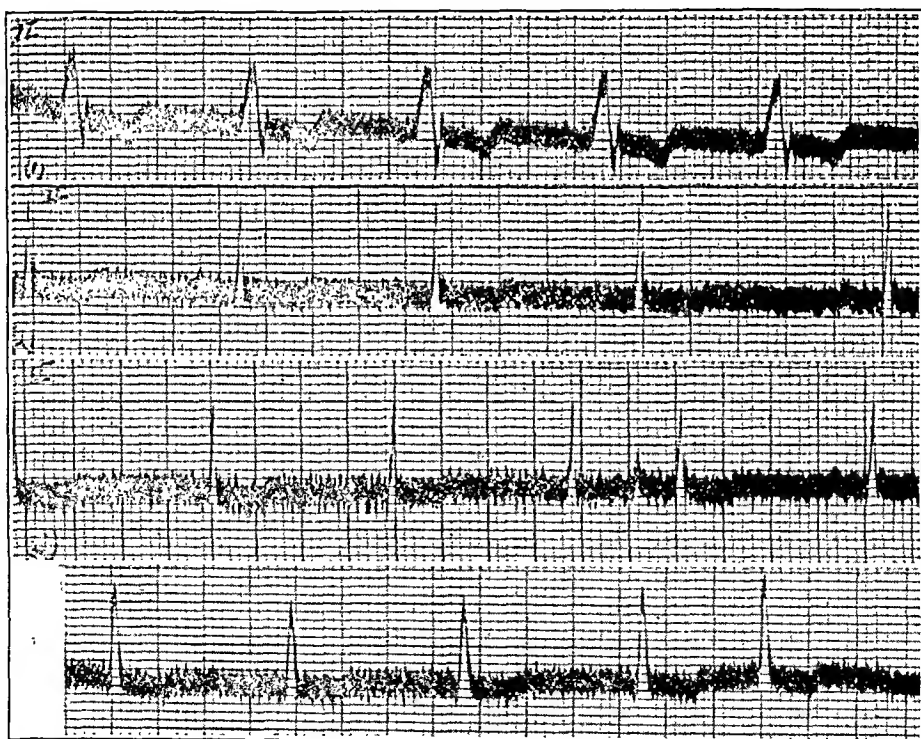


Fig. 7.—Record taken Feb. 27, 1929. All strips of Lead II: (1) persistent delayed intraventricular conduction. The rate was 79; QRS interval, 0.12 seconds; (2) taken after the administration of oxygen for five minutes with the patient at rest. There was normal intraventricular conduction. The rate was 70; the QRS interval, 0.07 seconds; (3) administration of oxygen continued but patient exercising. There was normal intraventricular conduction. The rate was 79; the QRS interval, 0.07 seconds.

ing inhalation of oxygen. Furthermore, during administration of oxygen, although the cardiac rate was increased by exercise, well above the point provoking delayed conduction in all previous observations, the normal appearance of the ventricular complexes was retained.

CONCLUSIONS

Faulty intraventricular conduction may in certain instances occur as a transient phenomenon. In this event it is not necessary to assume a permanent or complete anatomic interruption of the continuity of the bundle. It is more probable that in hearts exhibiting the phenomenon there is functional inefficiency in conduction which may yield ventricular complexes of aberrant form under the stress of greater demands on the myocardium. One of these demands is the necessity for more rapid ventricular output. Inhalation of oxygen may in such cases appreciably increase the ability of the bundle to conduct the excitatory stimulus.

DISEASE AND MAN. By GEORGE DRAPER. Price, \$4.50. New York: The Macmillan Company.

This is one of a series of books forming what is designated by the publisher "The Anglo-French Library of Medical and Biological Sciences." Each volume is published in both French and English with the hope that a closer bond between British and French men of science will thus be effected. Dr. Draper includes in the present volume much of what he has written in his "Human Constitution," certain previously published lectures and a sample clinic on constitution for students. Thus the whole work becomes a general treatise on constitution adapted more for medical students and practitioners than for advanced students of disease.

Draper feels that Man may best be described in four panels, each part necessary for a complete picture. These panels are termed the morphologic, the immunologic, the physiologic and the psychologic. The last named panel is perhaps stressed most in the present volume. One feels decidedly that in discussing the psychologic factors of man in relation to his diseases that the constitutionalist runs off the track of objectivity to which he has so conscientiously clung heretofore. The author forgets that the so-called "cure" of a patient by unearthing a repressed and painful early conflict from the patient's memory or subconsciousness, discussing it with him, and impressing him with its causal relationship to the complaint, does not prove that it actually is part of the cause. Following is one of Dr. Draper's examples: A woman had not been in good health or slept well for thirty years since the death of her baby whose every cry she had answered during its illness. On investigation the patient's bedroom was found to be next to an alley in which cats (baby's cry) howled each night. After realizing the similarity of the cry of the cats to her baby's cry, the patient slept soundly.

The author's discussion of the relation of morphologic characteristics to various disease types and his anthropometric studies are excellent. His consideration of the relations between sex and disease merits careful study. The work as a whole is well worth perusing.

THE EYE IN GENERAL MEDICINE. By A. MAITLAND RAMSAY. Price, \$5. New York: William Wood & Company.

This book, a second edition, the first having appeared in 1909, is divided into ten chapters which deal with: (1) the living eye considered as one of nature's laboratories; (2) the constitutional factor in disease, with special reference to some of the ocular manifestations of disordered carbohydrate metabolism; (3) some of the ocular manifestations of defective elimination; (4) the rôle played by the capillaries in the causation of disease, with special reference to the etiology of acute primary glaucoma; (5) the unification of physiologic and pathologic processes, with special reference to the muscle of the iris and the ciliary body; (6) the medical aspects of eye strain; (7) the offensive power of microbes and the defensive mechanism of the body, with special reference to pneumococcal ulceration of the cornea; (8) the reaction of the body to noxious agents, with special reference to toxic inflammation of the iris; (9) some ocular manifestations of cardiovascular disease, and (10) the importance of constitutional in addition to local treatment in many diseases of the eye.

The chapter on medical aspects of eye strain will call the reader's attention to the eye as a cause of symptoms which are not always associated with it, and may lead to speedier relief from symptoms when the possibility of eye strain is early called to the physician's attention. The argument in chapters two and three is rather far fetched and represents the author's ideas rather than those accepted by the medical profession at large.

The book, while interesting reading material, is too general, has little scientific value and cannot be recommended as a text on the relation of disease of the eye to systemic disease either to the graduate or the undergraduate in medicine.

THE VOLUME OF THE BLOOD AND PLASMA IN HEALTH AND DISEASE. By LEONARD G. ROWNTREE and GEORGE E. BROWN, with the Technical Assistance of GRACE M. ROTH. Price, \$3. Philadelphia: W. B. Saunders Company.

In this monograph, the authors present the results of their clinical studies of the blood and plasma volumes with the dye method of Rowntree, Keith and Geraghty.

The first four chapters are devoted to a discussion of the method, and careful consideration is given to the criticisms which have been made against it. From the evidence presented it seems justifiable to conclude that the method, while not ideal, is a practical procedure which should yield fairly reliable results. The reliability of the hematocrit readings has been increased by the adoption of Whipples' procedure involving the use of 1.6 per cent of sodium oxalate solution.

In chapter 5 are presented the values for seventy-four normal subjects. The remaining chapters are devoted to the consideration of the values obtained in 250 cases of various diseases. The authors have chosen to interpret their results on the basis of variations in the mean values for disease groups from the mean values for normal groups. In those instances in which the means are derived from very small series of cases the significance of moderate variations must be considered doubtful.

The book should stimulate the interest of clinicians in the further study of this important subject.

MODERN METHODS OF TREATMENT. By LOGAN CLENDENNING, M.D., Professor of Clinical Medicine, University of Kansas, with chapters on special subjects by several authors. Third edition. Cloth. Price, \$10. Pp. 815, with 95 illustrations. St. Louis: C. V. Mosby Company, 1929.

In this work, the author "planned to furnish an outline of all the methods of treatment used in internal medicine" and to "describe each method of procedure so clearly and minutely that a person who has never seen it performed could do it from the description." The first part of the book describes the procedure; the second part gives the indications for its application, based on the principles of physiologic pathology.

It is a rather ambitious undertaking for a single volume, and completeness and thoroughness have not been attained. However, the book contains an unusual amount of material of great practical value to the practitioner, and the style of presentation is interesting and clear.

The reviewer takes exception to the intravenous administration of epinephrine chloride, 15 minims (0.92 cc.) of a 1:1,000 solution in shock, collapse, pneumonia, etc., believing this to be not without danger and possibly to be lethal in action.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By THOMAS G. HULL. Price, \$5.50. Springfield, Ill.: Charles C. Thomas, 1930.

The material contained in the 303 pages of text is arranged in five sections which deal with diseases of domestic animals and birds, rodent infections, human diseases spread by animals, animals as passive carriers of disease organisms and the rôle played by each animal in the spread of disease. Tuberculosis, anthrax, foot and mouth disease, Malta fever and contagious abortion, milk sickness, actinomycosis, smallpox and chickenpox, glanders, rabies, psittacosis, food poisoning, swine erysipelas and diseases caused by animal parasites are discussed in the first section; plague, tularemia, spirochetal jaundice, rat-bite fever and Rocky Mountain spotted fever in the second; botulism, tetanus and gas gangrene in the third; the relation of human infections to infections in animals, septic sore throat, diphtheria, scarlet fever and other human diseases sometimes contracted by animals in the fourth; and the rôle of cattle, horses, swine, sheep, goats, dogs, cats, rats and mice, poultry, birds and wild game in the fifth.

The chapters state briefly the essential facts and stress the epidemiologic importance of the diseases.

The book is of value to those seeking general information of this character rather than detailed data of a strictly scientific nature.

THE CHEMICAL ASPECTS OF IMMUNITY. By H. G. WELLS. Revised edition. Monograph Series, No. 21. Price, \$6. New York: The Chemical Catalog Company.

A book of the type which Wells has written can be written only by one who is thoroughly conversant with both chemistry and immunity; a book that is so easily read can be written only by one who can clearly differentiate the essential from the less essential; a book that is so concise and so condensed can be written only by an experienced teacher. While the reviewer may find no great alterations from the first edition, the revision takes cognizance of practically all the recent developments in immunology. Thus Wells definitely puts aside the lipoids as antigens—this in line with the consensus of most immunologists. Of course, such rejection by no means lessens the importance of the lipoids in many immunologic processes because of their rather diverse physical properties. As one of a series of monographs issued by the American Chemical Society the book fulfils every requirement that can be demanded by the title. It is remarkably short; it is clear, and it is accurate, and for this reason it is of value not only to the chemists who wish a superficial orientation but even to the immunologists who may desire a rapid survey of a certain field. It is to be regretted that one cannot so characterize medical books more frequently.

A PATIENT'S MANUAL OF DIABETES. By HERBERT W. MOXON. Price, \$2.25. New York: William Wood & Company, 1929.

With so many excellent manuals already on the market, any new contribution to this field should possess some exceptional quality to justify its presence. In this manual the author seeks, in the earlier chapters, to give the patient a more complete understanding of the disease and the principles which underlie its treatment than do other texts of this type. These chapters are excellent and should serve their purpose well. Particularly good are the two in which a comparison is made for the patient of the working of the human engine in health and in diabetes. The remaining chapters differ little from similar ones in other publications of this type, except for the descriptions of the Line-Ration system of R. W. Lawrence and the Five-Gram Diet scheme of L. A. Harrison. These systems are little used in this country.

glass tube (fig. 1) which led the two ends to the surface; a purse string suture closed the pericardial incision and at the same time included the flange of the glass tube, thus fixing the tube in place. The proximal end of the tube was sutured in the wall of the chest, and the incision was closed, care being taken to remove any pneumothorax.

After three or four hours the animal had completely recovered from the anesthesia, was active, showed little shock from the operation and apparently suffered no pain. By fixing of the external portion of the glass tube and drawing lightly on the ligature, the artery and included tissue, which usually includes also the accompanying vein, were compressed.

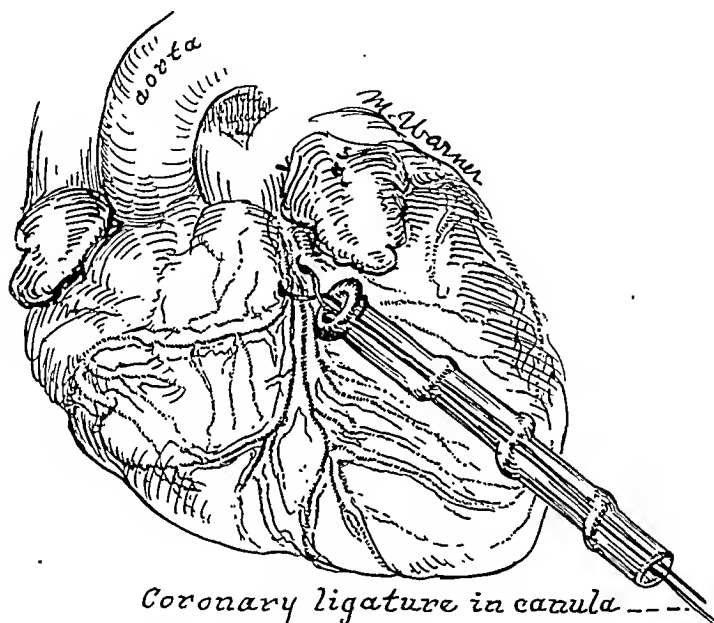


Fig. 1.—Coronary ligature and glass cannula.

This series of dogs was prepared as described, by passing a ligature around the ramus descendens anterior sinister, through a glass tube, and allowing the animal to recover completely from the anesthesia.

Dog 1.—The operation was performed as described. Three hours after operation the dog had completely recovered from the anesthesia, was active and showed no evidence of pain; it lay quietly while the dressings were removed and the tube was manipulated. Pulling on the tube with displacement of the pericardium produced no pain. Slight traction on the ligature caused uneasiness with stiffening of the legs, especially the left foreleg; moderate traction produced restlessness and whining, and strong traction sufficient to occlude completely the artery produced restlessness and other evidences of severe pain. During this period salivation was marked.

Numerous repetitions always gave the same results. The pain began immediately on beginning of traction and ceased promptly with its release. Finally, too strong traction was made so that the artery was torn in two. The pain promptly ceased.

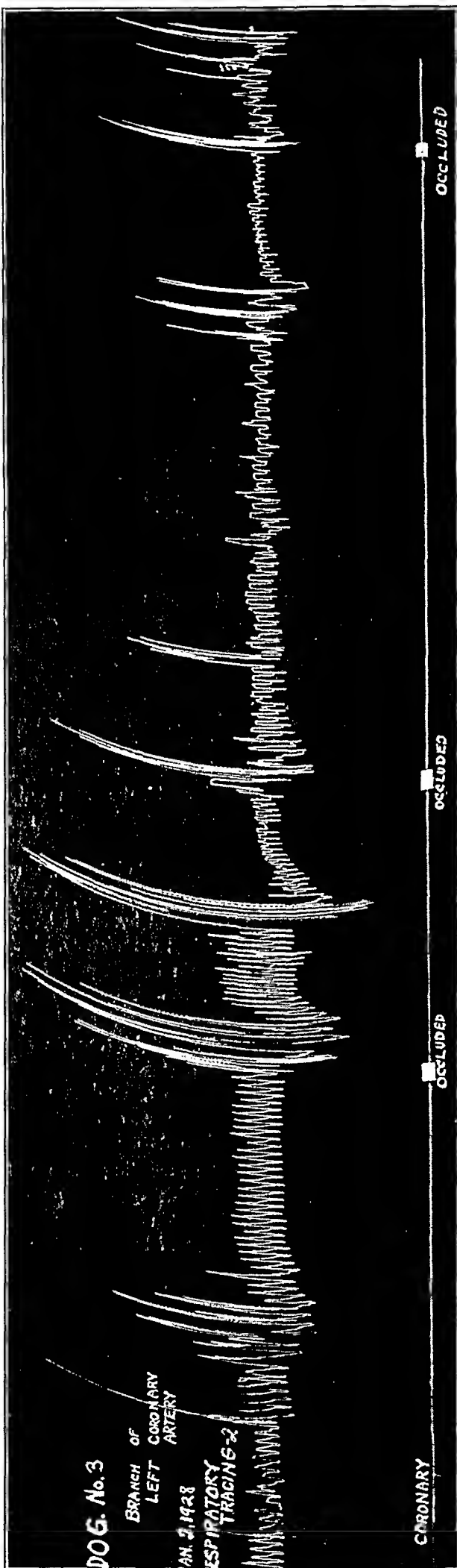


Fig. 2.—Respiratory effect of temporary occlusion of ramus descendens anterior sinister in dog 3.

Dog 7 A.—On March 10, 1928, the annulus of Vieussens was removed under general anesthesia. The dog recovered without any complications. On March 24, the dog was prepared as those in the preceding experiments, and after four hours had completely recovered from the operation and showed no symptoms when either the wound or the tube was handled. Traction repeated many times invariably failed to produce pain. The dog was allowed to remain alive until March 27, during which time repeated attempts to produce pain by traction on the ligature resulted in failure. On opening the chest under general anesthesia the heart was found to be moderately dilated, local pericarditis was present at the point of the opening and the ligature was found to include the artery and vein one-half inch from the origin of the ramus descendens anterior sinister.

Dog 7 B.—On March 17, 1928, the annulus of Vieussens was removed, the dog making a complete recovery without infection. On March 31, the dog was prepared as in the preceding experiments, three and one-half hours being allowed for recovery. In this animal, repeated attempts to produce pain by traction on the ligature resulted in failure. Pulling on the tube so as to stretch the parietal pericardium and displace the heart produced no pain. Salivation at times was marked during stretching. Under general anesthesia the chest was opened; the heart was found to be moderately dilated and the ligature was around the artery and vein at the origin of the artery.

Dog 9 A.—On March 31, 1928, the annulus of Vieussens was removed, the wound healing without infection. Seven days later the chest was opened as in the preceding experiments, and the ligature was passed around the artery. On repeated traction, no pain was produced. The chest was opened under general anesthesia, and the heart was found to be moderately dilated. The ligature was about one-half inch from the origin of the artery.

Comment on Results of Temporary Occlusion.—As previously stated, after the animal has recovered from the effects of the anesthesia, it is in surprisingly good condition. In the opening of the chest, muscles are displaced without being cut or torn, so that on recovery respiration and use of the limbs seem to cause no pain. Manipulation of the slightly protruding glass tube produces no pain.

Pulling the tube through the wall of the chest so that the parietal pericardium is stretched produces no pain. Pulling until the heart is displaced produces no pain.

The effects of compression of the artery are:

1. The moment the lumen of the artery is narrowed there is distinct evidence of pain, shown by restlessness of the animal. This pain ceases immediately on the return of the artery to its normal size.

2. Increasing narrowing of the arterial lumen produces increasingly severe pain, until total occlusion produces apparently severe pain. This disappears immediately on the release of occlusion.

3. As shown in dog 8, apparently the pain varies not only with the degree of obstruction but also with the size of the vessel occluded, being increased in severity by increase in the size of the artery.

be due to the anastomosis between the anterior descending and the circumflex artery.

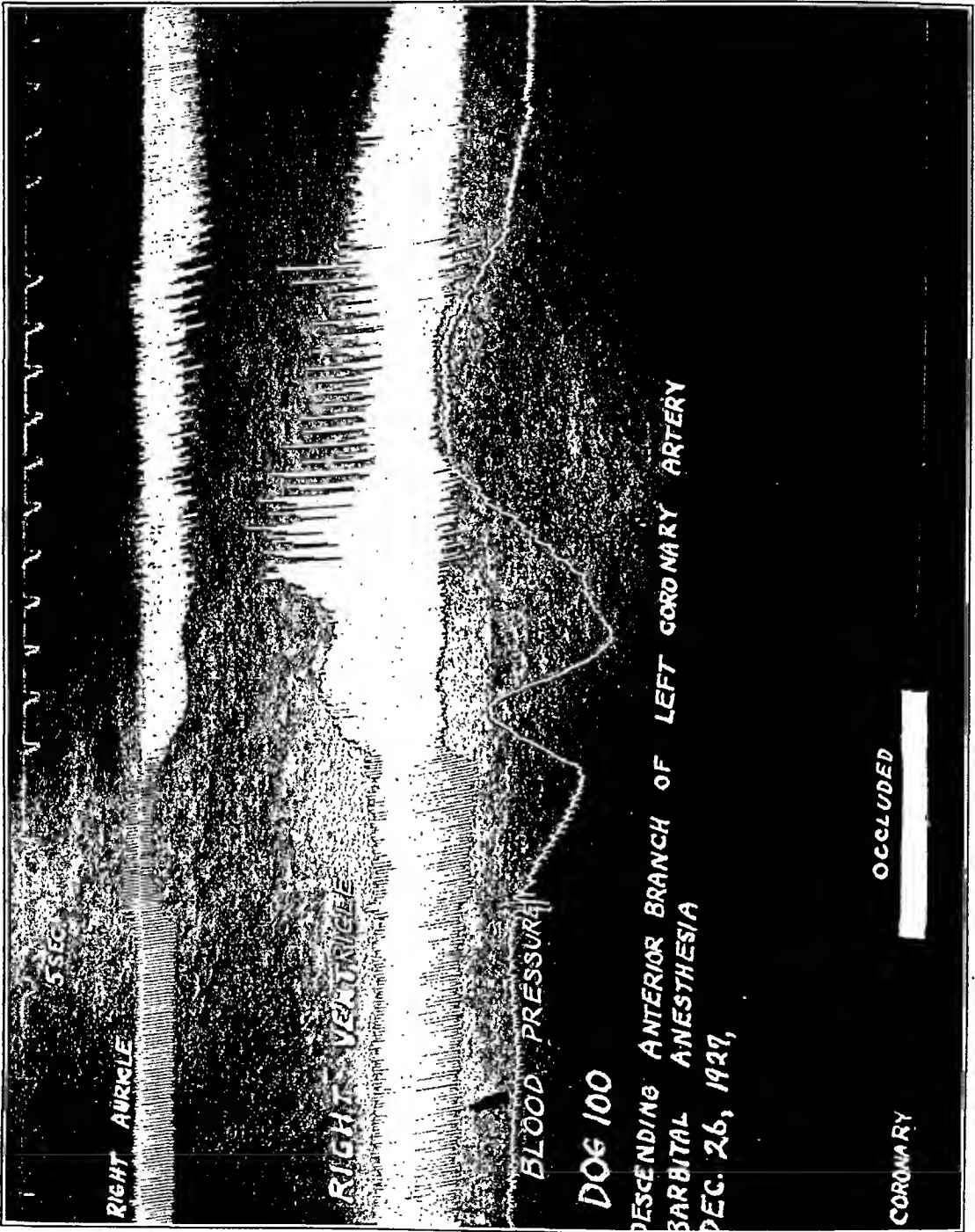
It has also been observed in experiments not here recorded that anoxemia during the period of anesthesia or from pneumothorax greatly increases the degree of dilatation following partial or complete occlusion of the ramus descendens anterior sinister.

Electrocardiographic studies made on the dogs with intact extrinsic cardiac nerves during periods of temporary traction show first a pause, followed by premature contractions, usually of ventricular but occasionally of auricular origin. At the beginning of traction, complete cardiac standstill has occurred for periods of from one to five seconds. Short periods of paroxysmal tachycardia have occurred, and on one occasion temporary occlusion produced an auricular fibrillation. There is a marked increase in the amplitude of both the R and the T waves. Inversion of the T wave has been observed only once; but in all cases it arises before the end of the down stroke of the R, as occurs in electrocardiograms after coronary occlusion in human beings.

THE PHYSIOLOGIC EFFECTS OF TEMPORARY OCCLUSION OF THE CORONARY VESSELS IN THE ANESTHETIZED DOG

For direct observation of the heart, a second series of experiments was done in which light barbital anesthesia and artificial respiration were used. The chest was laid open and the parietal pericardium was incised, the entire heart being exposed. The heart was kept moist with warm physiologic solution of sodium chloride. Myocardiographic levers were attached to the apex of the right ventricle and the left auricular appendage, and led to tambours writing on a smoked drum. The blood pressure was recorded directly from the left carotid artery by means of a mercury manometer. A ligature was passed around the coronary artery and through a glass tube which was inserted through a stab wound of the wall of the chest, exactly the same procedure as used in the preceding experiments. This technic enabled the direct observation of the changes in size, color and rhythm of the heart, also the recording of the ventricle and auricle, with simultaneous blood pressure curve.

Dog 100.—With the dog under barbital ether anesthesia, the chest was opened. Myographic levers were attached to the apex of the right ventricle and the end of the left auricle. The blood pressure was taken from the left carotid. A ligature was passed around the ramus descendens, one-fourth inch below its origin, as previously described. Traction produced a decrease in amplitude followed by an increase; the rate was slowed, then increased and irregular. The ventricular rate was increased with marked variation in amplitude. The blood pressure fell at times from 30 to 50 mm. of mercury. Immediately at the beginning of traction the vein included in the ligature became distended, the apex became first cyanotic, then pale, with a rapid increase in both auricular and ventricular volume.



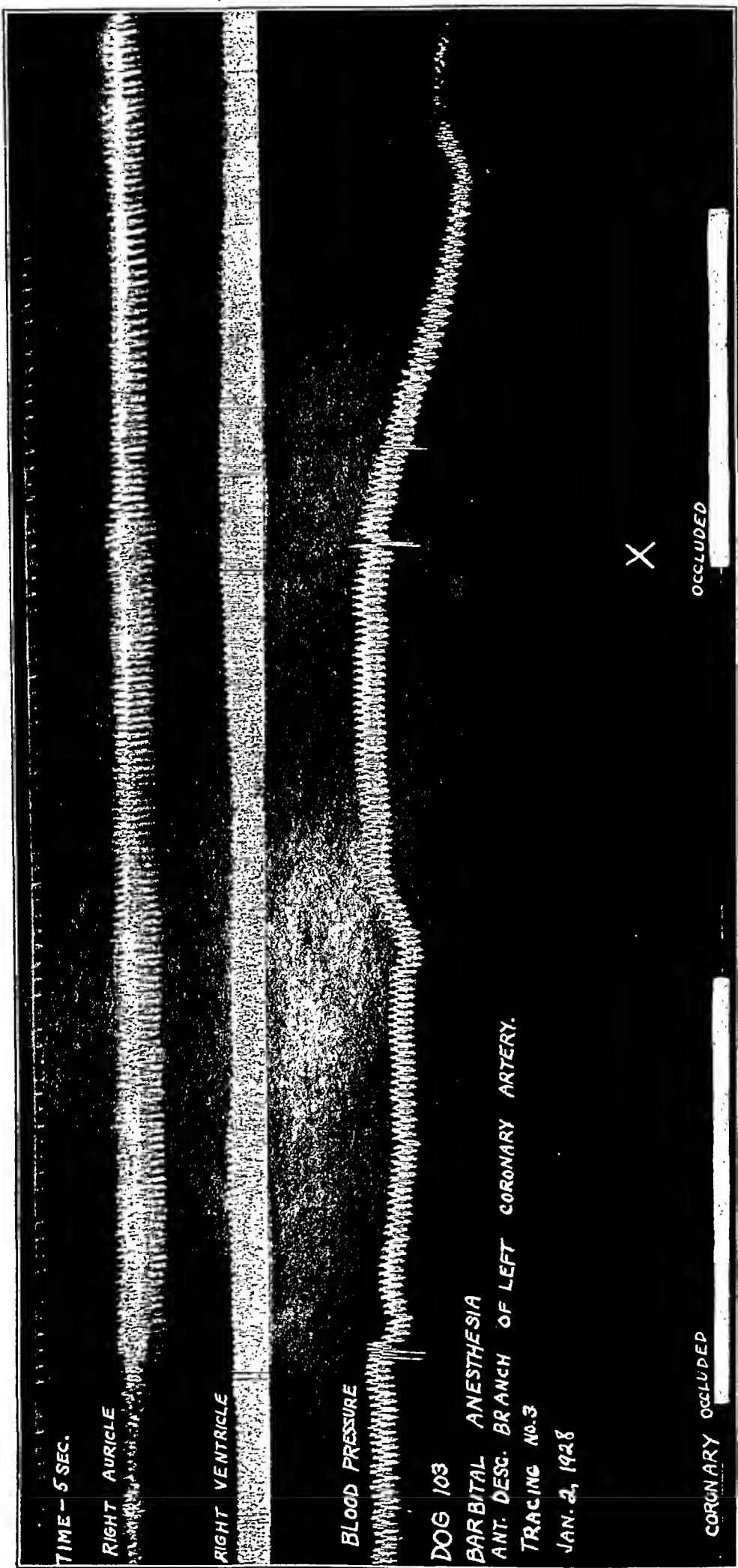


Fig 4.—Curve for dog 103. First gradual fall of blood pressure of 60 mm. of mercury. Note ventricular standstill at beginning of occlusion.

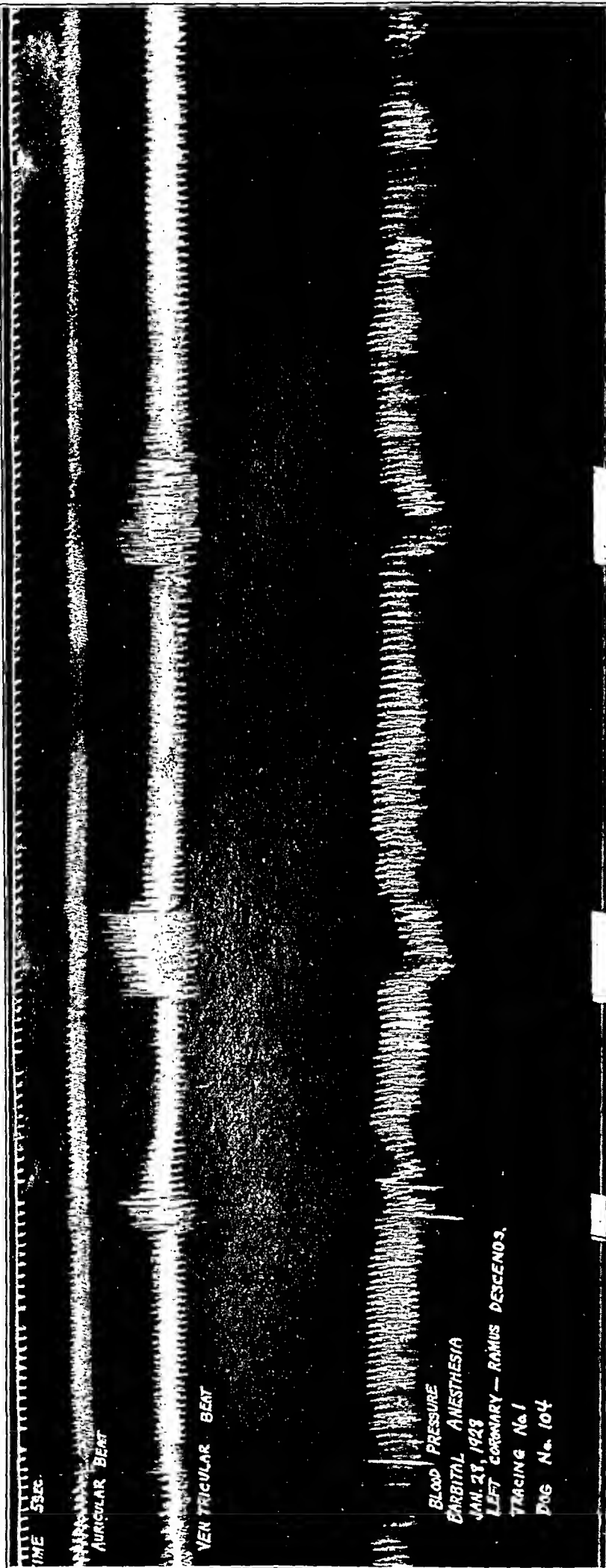


Figure 5

pression of the vessel. To exclude the possibility that this pain is produced by compression of nerve trunks that are closely associated with the vessels or their surrounding tissue, the ramus descendens anterior sinister is carefully dissected out over a short distance near its origin and painted with 80 per cent alcohol, which is not allowed to spread over the surrounding tissues. The ligature is passed around the artery, as described previously and passed through the tube; the pericardium and the wall of the chest are sutured, and the dog is allowed to recover from the anesthesia.

Dog 200.—With the dog under ether anesthesia, the ramus descendens anterior sinister was dissected out as already described, the wall of the artery was painted with alcohol and the animal was allowed to recover. Repeated traction with temporary occlusion of the artery failed to produce pain. The location of the ligature was verified by autopsy, and the heart was found to be moderately dilated.

Dog 201.—Under preparation as in the preceding experiment, the artery and vein accompanying were separately dissected out, individual ligatures being passed around each. The artery was painted with alcohol and the wall of the vein was left uninjured except for the trauma of dissection. Repeated traction on the artery failed to produce pain. Repeated traction on the vein produced moderate pain. The location of the ligature was verified by autopsy.

Dogs 202 and 203.—These animals were prepared as in the preceding experiments, the artery being dissected out and painted with 80 per cent alcohol. The animal was then allowed to recover. Repeated traction failed to produce pain. Dog 202 was markedly salivated during traction. In both dogs subpericardial injections of 10 per cent solution of ammonium hydroxide were introduced through a long needle passed into the glass tube. These injections failed to produce pain. The heart muscle was also perforated at a number of points with a coarse wire passed through the glass tube, without the production of pain.

Dogs 204, 205 and 206.—These animals were prepared as in the preceding experiments, the artery in all cases being painted with alcohol. Repeated traction on the ligatures failed to produce pain. These dogs were also given subpericardial injections of 80 per cent alcohol and 10 per cent ammonium hydroxide, without the production of pain. The mechanical perforation with a large needle also failed to produce pain. These procedures were carried out through the glass tube.

Dogs 207 and 208.—In these animals the artery was dissected out and the ligature applied as in the preceding experiment, but without the application of alcohol. On traction pain was produced as in all experiments of occlusion of the coronary. From 2 to 3 drops of alcohol were then applied to the denuded area of the artery by passing a long needle through a glass tube. After a few minutes, traction on the ligature no longer produced pain.

Dogs 209 and 210.—The ramus descendens anterior sinister was dissected out, the ligature passed around the artery and the animal allowed to recover. Traction in each of these dogs produced immediate pain, which disappeared on release of traction. Introducing a large needle through the glass tube, a drop of 80 per cent alcohol was applied to the artery at the point of ligature. Five minutes later traction failed to produce pain. One of these dogs was salivated during traction.

Dog 301.—The animal was prepared as was dog 300. Mercury was injected into the artery one-fourth inch from its origin. Recovery was uneventful, apparently without pain. Four hours after anesthesia the animal was able to run indefinitely with apparently no inconvenience. At autopsy no mercury was found in any of the vessels, but there was a firm thrombus at the point of injection, and the area supplied by the artery showed a definite anemic infarct.

These experiments demonstrate that continuous occlusion of the coronary by a thrombus in the dog failed to cause objective evidence of continuous distress. Judging from the preceding experiments, these animals must have been distressed for a short period after the occlusion, which was not evident because of the anesthesia. These experiments, however, did not assist in answering the question of whether the pain on occlusion by compression was due to the obstruction per se or to the compression of nerves.

So, in a series of several dogs, in six of which success was obtained, one or the other coronary artery was blocked at its origin by the passing of a wire with a small knob on its end down the left carotid artery through the aorta and into either the left or the right coronary opening. Various wires have been used, the most satisfactory being a brass rod slightly smaller than the carotid. The end that is passed into the carotid is bent slightly, three eighths of an inch from the tip. Porter,³ with the subject under ether anesthesia, introduced a glass rod⁴ bent slightly at the top and introduced through an incision in the innominate artery. He said:

The rod is passed down toward the left anterior sinus of Valsalva. As soon as the resistance of the aortic valve is felt, the rod is withdrawn a little and its head made to traverse the aortic wall near the bottom of the sinus. The opening of the left coronary artery will presently be found. Into this the rod is passed and fastened in place by tying a ligature around the innominate artery, including the rod. . . . Closure of the artery was always promptly followed by arrest. Fibrillary contractions were present in every case but one. . . . It seems hardly possible that the gentle introduction of the glass rod into the artery could in any way injure the artery.

METHOD

By our method, with the subject under procaine hydrochloride anesthesia the left carotid is dissected out and separated from the vagus nerve. Through an incision in the arterial wall the rod is passed carefully until it impinges on one of the aortic cusps. This is recognized first by ascertaining the length of the rod that will reach the cusps, and second, by the resistance encountered and the forceful pulsations that

3. Porter, W. T.: Further Researches on the Closure of the Coronary Arteries, *J. Exper. Med.* 1:46, 1896.

4. The first mention of Porter's method was made in the *Zentralbl. f. Physiol.*, 1895, no. 16, p. 481.

and connecting it with a recording mercury manometer. When the rod was passed down into the ascending aorta and turned so as to pass into the left coronary orifice, evidence of pain was produced with violent respiration, marked elevation and variation in blood pressure, followed by a rapid fall and death of the animal.

Examination of the heart and aorta showed the rod occluding the left coronary artery (fig. 7).

One of us (D. C. S.) once stood at the bedside of a young man who suddenly clutched his chest and with a look of anguish died. Autopsy revealed a large embolus completely occluding the orifice of the left coronary artery.

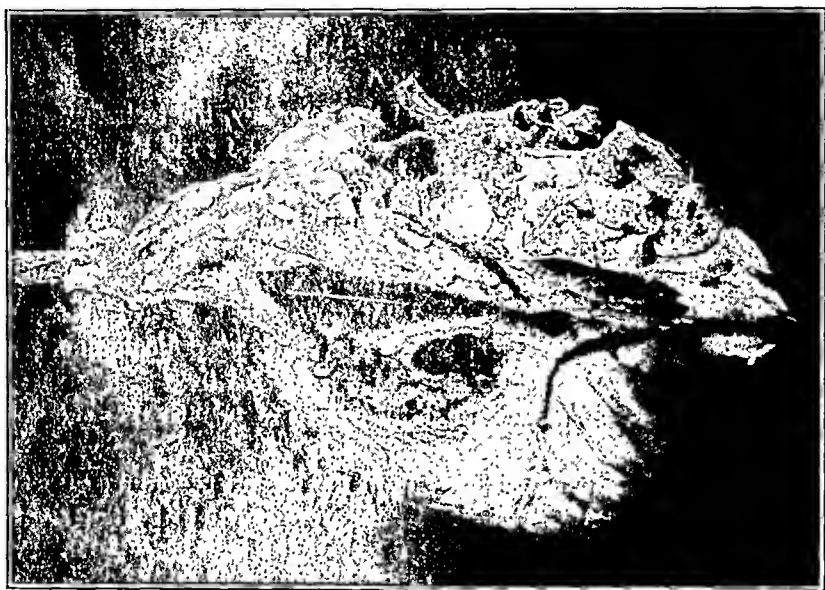


Fig. 6.—Rod inserted through the carotid and aorta into the left coronary artery and down the circumflex until it bulges out the pericardium.

Experiments on dogs 501 and 502, concerning which there might be some doubt because the coronary orifice was not found occluded at autopsy, undoubtedly were examples of true occlusions.

Repeated failures in which the aorta and heart were injured or perforated never showed the symptoms observed in coronary occlusion.

In the experiments in which a ligature was passed around the coronary artery and vein, on one occasion both were missed, and it was found that traction on the ligature did not produce pain. This was followed by passing the ligature through various portions of the anterior surface of the heart without the inclusion of vessels, with the result that traction or even tearing out of these ligatures in the conscious dog produced no pain. This apparent absence of pain from

mechanical stimulation of the myocardium and visceral pericardium was checked by further observations.⁵

These experiments were done either through a glass tube sutured into the pericardium as in preceding experiments or by injecting local anesthesia into the wall of the chest of the dog over the third, fourth or fifth interspace, a needle being passed directly through the chest and into the myocardium. The location of the puncture made in the myocardium was invariably checked by postmortem examination (fig. 8).

In dogs 204, 205 and 206 (the preceding protocols) the muscle and visceral pericardium was pierced at a number of points with a large hypodermic needle or a blunt wire through the glass tube already fixed in place. In four dogs a large hypodermic needle was introduced through the intact thoracic wall (local anesthesia having been induced in the skin and subcutaneous tissues). No pain was noted after the pleura was passed. Just as the heart was touched near the apex, occasional pain had been noted. This is interpreted as occurring at the moment of piercing the parietal pericardium.

In eleven dogs in which passing of the rod into the orifice of the coronary artery through the aorta was attempted, or in the use of the aortic dilator, accidental puncture of the heart muscle occurred. In

5. Willis, R.: *The Works of William Harvey*, printed for the Sydenham Society, London, 1847, p. 383. It is of interest to note that Harvey probably was the first to discuss sensation in the heart. A young nobleman, following a fracture of the ribs, had a large abscess which opened, leaving a large gaping wound on the left side. Charles I asked Harvey to see him and report on the case.

Harvey found an extensive ulcer, "into which I could readily place three fingers and a thumb. Which done, I straightway perceived a certain protuberant fleshy part, affected with an alternating extrusive and intrusive movement. This part I touched gently. Amazed with the novelty of such a state, I examined everything again and again, and when I had satisfied myself, I saw that it was a case of old and extensive ulcer, beyond the reach of art, but brought by a miracle to a kind of cure, the interior being invested with a membrane, and the edges protected with a tough skin. But the fleshy part (which I at first took for a mass of granulations), and others had always regarded as a portion of the lungs, from its pulsation motions and the rhythm they observed with the pulse—when the fingers of one of my hands were applied to it, and those of the other at the wrist—as well as from their discordance with the respiratory movements, I saw no portion of the lung that I was handling, but the apex of the heart covered over with a layer of fungous flesh by way of external defense, as commonly happens in old foul ulcers.

"Instead of a verbal answer, therefore, I carried the young man himself to the king, that His Majesty might with his own eyes behold this wonderful case; that, in a man alive and well, he might, without detriment to the individual, observe the movement of the heart, and, with his proper hand even touch the ventricles as they contracted. And His Most Excellent Majesty, as well as myself, acknowledged that the heart was without the sense of touch; for the youth never knew when we touched his heart, except by the sight or the sensation he had through the external integument." This is truly a royal experiment.

In three dogs, through local anesthesia of the skin, epinephrine, 1:1,000, was injected subpericardially, near the apex.

Dog A received an intramyocardial injection of 0.5 cc. of epinephrine near the apex, within a moment stood still, semirigid as if in pain, the left foreleg limped distinctly when forced to walk (the thoracic puncture of the preceding dogs did not produce this limp), soon vomited, and within ten minutes was apparently well. Two more injections of 0.5 cc. produced all the preceding symptoms except the limp on walking.

Dog B was given two injections into the myocardium of 0.5 cc. of 1:1,000 epinephrine, which resulted in a semirigid position following the injection, vomiting, but no disturbance of gait.

Into dog C, 1 cc. of 1:1,000 epinephrine was introduced through a locally anesthetized area of the thorax. This was injected in small amounts through several punctures into the myocardium. This animal suffered definite pain, limped with the left foreleg and vomited. Within ten minutes the animal was anesthetized and the heart was removed. An area 2.5 cm. in diameter of localized ischemia was found.

The interpretation of this experiment is modified by the fact that the injection of epinephrine into the heart muscle is absorbed almost as rapidly as an intravenous injection. The semirigid position of standing and the vomiting are probably due to the general effect of the epinephrine.

The limp of the left leg on two occasions can be interpreted only as referred pain from the myocardium. The pain shown by dog C is comparable to that of the closure of a small branch of the coronary artery.

In two dogs, injection of from 3 to 4 cc. of normal physiologic sodium chloride (with the idea of stretching the visceral pericardium) failed to elicit pain.

The pulling on the glass tube which was sewed into the pericardium of the dog resulted in no pain due to displacement of the heart or stretching of the pericardium.

In one monkey (*Macacus phenur*) the ribs and sternum lying immediately anterior to the heart were dissected away under local anesthesia, and the pericardium was incised, the heart being held toward the anterior wall of the chest by two fine forceps applied to the parietal pericardium. There was apparently no pain noted as a result of traction on the parietal pericardium. It was noted that when the forceps were clamped to the parietal pericardium, evidence of pain was elicited. Using a fine pair of forceps, pinching of the visceral pericardium of the anterior surface of the heart resulted in no evidence of pain. The heart was too small to pass the usual ligature. With a fine forceps, pinching of the circumflex branch of the coronary artery produced the same pain as in other methods of temporary occlusion. When the

tissues superficial to the artery were pinched without blocking the artery, no pain was produced. (Only one monkey was used as a check, as the results were entirely comparable with those found in dogs.)

SUMMARY AND CONCLUSIONS

It has been definitely shown that temporary partial or complete interference with blood flow in a coronary artery or vein invariably produces pain. This pain is apparently referred to the foreleg, as shown by: (a) rigidity of the left foreleg when the ramus descendens anterior sinister is ligated or temporarily occluded; (b) limping of the left foreleg after repeated temporary occlusions of the ramus descendens anterior sinister, and (c) limping of the left foreleg in two animals after intramyocardial injection of 0.5 and 1 cc. of 1:1,000 epinephrine. It is certain that this limp is different from that which occurs as the result of injury to the wall of the chest from the operation.

The nerve fibers responsible for conducting the pain sensations from the heart are those fibers in the adventitia of the blood vessels or adjacent tissues. This is indicated by the absence of pain after painting the stripped arterial wall with 80 per cent alcohol.

The tearing of the artery or veins also severs the nerve pathway, resulting in disappearance of the pain.

The pain is not produced by sudden distention of the arterial wall proximal to the point of occlusion, as closure of the orifice in the aorta produces pain without distention. Occlusion of the orifice also eliminates pressure on the nerves included in the ligature as a cause of pain.

The pain pathway to the brain is by way of the sympathetic, as shown by the presence of pain when the vagi are severed, and its abolition by removal of the stellate ganglion or the annulus of Vieussens.

Nausea, as evidenced by salivation in the dog, and actual vomiting have occurred as a result of temporary occlusion of the coronary artery. This occurred in two instances when the sympathetic pathway was interrupted, and possibly verifies the observations of Thatcher, that vomiting may occur reflexly from the heart.

Although the microscopic anatomy of the visceral pericardium shows a marked network of nerve plexuses which have been interpreted as sensory nerves, our experiments have failed to show any evidence of sensory nerves.

As shown by traction on the glass tube fixed to the parietal pericardium of dogs, (a) stretching of the parietal pericardium does not produce pain; (b) displacement of the heart does not produce pain, and (c) displacement of the aorta does not produce pain until the surrounding structures are disturbed.

On the other hand, evidence is shown directly in the monkey that mechanical stimulation of the parietal pericardium produces pain. Capps⁶ has made similar observations in man.

From the evidence presented, the only cause of pain in the myocardium and visceral pericardium is the result of interference with the blood supply. This is in accord with the original theories of angina pectoris as expressed by Hunter, Jenner, Parry and others. The original theory presumes that interference to blood supply results from narrowing of the arterial lumen as in arteriosclerosis. Later the theory of vascular spasm (Blackhall, See, Huchard) was advanced to explain those cases in which no anatomic vascular changes are found, which results in the same interference with nutrition of the heart muscle.

Our experiments indicate that angina pectoris (or cardiac pain) is the result of insufficient nutrition to the heart muscle. This being true, it is readily conceivable that the anatomically normal heart may, under conditions of extreme exertion, fail to receive sufficient blood (nutrition) through normal coronary arteries. In fact, this is suggested in the sensations of athletes just before getting their "second wind." These sensations are choking sensations, substernal oppression or actual precordial or substernal pain.

Untrained subjects may experience sensations so severe as to prevent continuance of the efforts until the "second wind" comes. If intelligent patients suffering from angina pectoris are carefully questioned, a surprising similarity between the sensations of an extreme effort in youth and their present sensations during an attack of angina pectoris of effort is found. This similarity was first called to my attention (D. C. S.) by the unsolicited observation of a patient that the sensation felt as a young man after running up a mountain side, during an emergency, was exactly the same as that now felt during an attack of angina pectoris.

Wenckebach⁷ drew similar conclusions in discussion of the "Töten Punkte" ("second wind") and angina pectoris. He further called attention to the fact that both are relieved by the administration of nitrites.

However, in hearts in which the blood flow is decreased by sclerotic narrowing of the lumen of the coronary arteries, much less exertion may result in sufficient interference with the blood flow to cause pain. In some cases there are apparently no or insufficient changes in the coronary arteries of persons who have suffered from angina pectoris during life to account for the pain as an obstructive phenomenon. In these cases a spasm of the coronary arteries has been presumed to exist, although sclerosis of the smaller vessels has not been excluded.

6. Capps, J.: *Tr. A. Am. Physicians* 42:243, 1927.

7. Wenckebach: "Töter Punkt" — "Second Wind" and Angina Pectoris, *Wien. klin. Wchnschr.* 41:1, 1928.

Anoxemia as the result of pulmonary lesions, as emphysema, results in a constant undernutrition of the heart muscle, making it more susceptible to the effects of decrease in blood supply. It is well known that irritability of nerve endings is increased by lack of oxygen, but that they are anesthetized by prolonged asphyxia.

PAIN IN THE AORTA AND EFFECTS OF MECHANICAL DILATATION OF THE AORTA

Vaquez, Allbutt and others have suggested the hypothesis that the pain of angina pectoris is produced by dilatation of either the first portion of the aorta or the aortic ring. This theory is attractive and has been widely accepted because of the frequency of attacks of angina and spasmodic dyspnea in syphilitic aortitis and the aortitis following influenza.

We thought that it might be possible to test the theory experimentally. Accordingly, through the designing of an instrument that is best described by illustration (fig. 9), it is possible to stretch the aorta and aortic ring and other vessels, only local anesthesia being used for

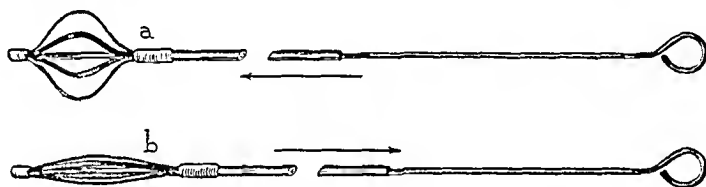


Fig. 9.—Aortic dilator (*a*) distended and (*b*) closed.

the insertion of the instrument into the artery. As in the experiments in which a rod is passed into the coronary orifices, the left carotid is dissected out under local anesthesia and freed from the surrounding tissue, especially the vagus nerve, with the minimum of injury.

UNANESTHETIZED DOGS

In a group of nine dogs under local anesthesia the left carotid artery was exposed, and isolated and incised to introduce the aortic dilator. It is noted in all dogs that although there is some stretching of the carotid artery as a result of the size of the dilator, there is no objective evidence of pain as the result of forcing it through. The junction of the carotid and aorta at times offers resistance to the passage of the dilator. In no instance was pain observed as a result of passing this obstruction. The ascending portion of the aorta is located by passing the instrument onward until the tip impinges on the aortic valves. It is drawn from one-fourth to one-half inch away from the valves, so as to avoid stretching the aortic ring. At this point, the dilator is extended fully.

In no instance did stretching of the aorta produce any evidence of pain, although at postmortem examination the intima was found to be torn and lacerated as a result of the tension of the springs. Passing the dilator through the aortic ring, which is estimated by the distance the tube passes after impinging on the valves and dilating the

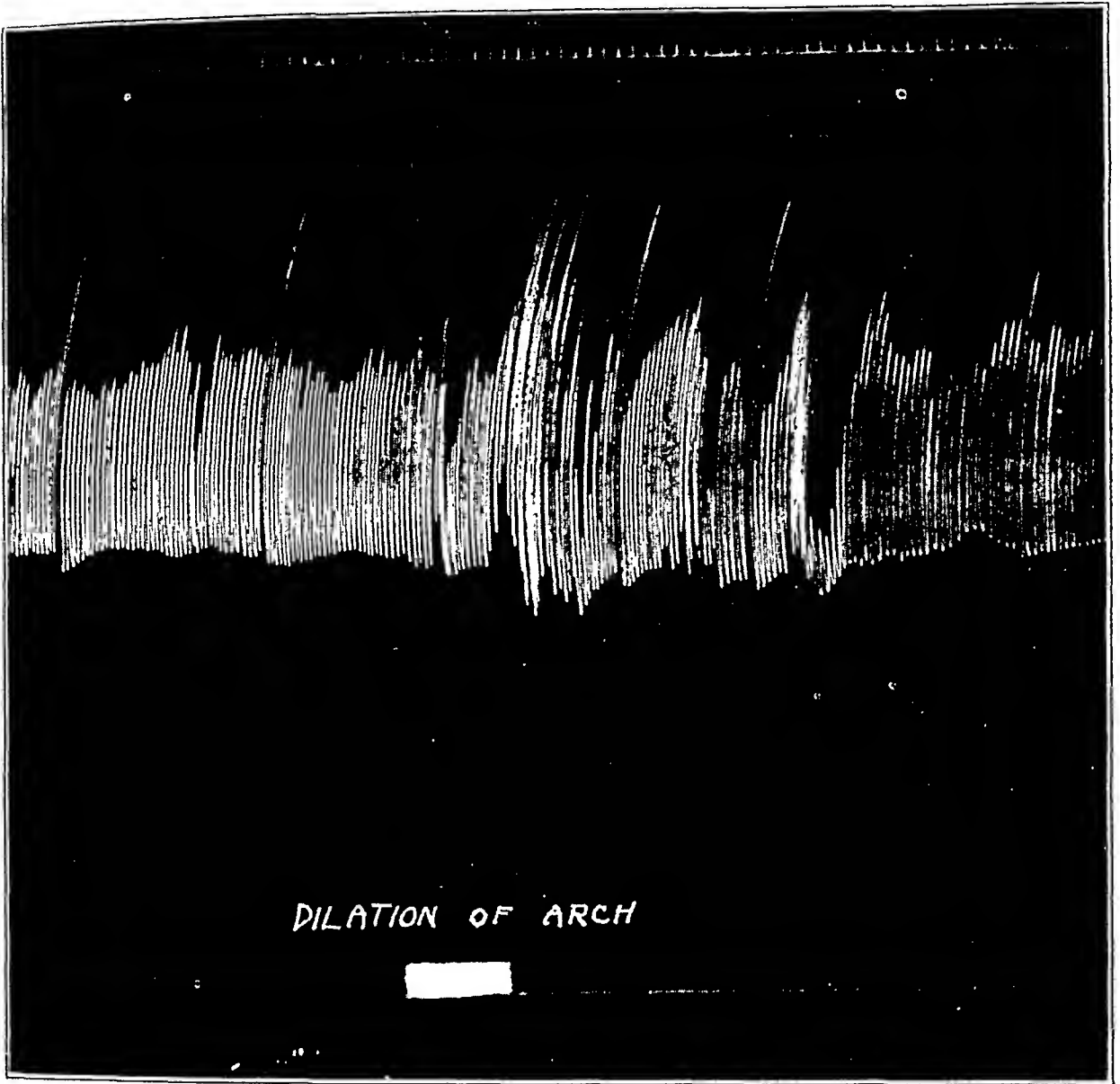


Fig. 10.—Tracing showing respiration in dog 30 with dilation of arch of aorta.

ring, fails to produce pain. Passing the instrument on into the ventricle, extending the dilator in the ventricle, produces no evidence of pain.

Stretching of the ascending aorta, aortic ring and cavity of the left ventricle always produces a marked spasmodic dyspnea. This ceases on release of the stretching (fig. 10).

When the tip of the dilator impinges on the aortic cusp, considerable pressure can be used before the cusp is perforated. The longitudinal

stretching of the aorta as a result of pressure on a cusp of the valve causes no pain. A spasmodic dyspnea is produced by longitudinal stretching.

Perforation of an aortic valve cusp produces no pain. The spasmodic dyspnea ceases as soon as the stretching of the aorta is relieved by the tearing of the cusp.

In the experiments on occlusion of the coronary artery through the aorta, the rod was pressed firmly against the aortic wall, mechanically irritating and tearing the intima, without production of pain. Also, in the attempts to occlude the orifice of the coronary and in the present experiment, the aorta was perforated either by too great pressure or by the breaking of the springs of the dilator.

As the result of these accidents, the following points have been perforated: (1) the carotid, at the junction of the aorta; (2) the arch opposite to the origin of the carotid; (3) the ascending aorta, and (4) the aortic ring. No immediate pain is noted as a result of perforation of the aorta. Later hemorrhage into the surrounding tissues produces spasmodic dyspnea and pain.

ANESTHETIZED DOGS

For the purpose of studying the effect on blood pressure, a group of dogs was prepared as in the preceding experiment, general instead of local anesthesia being used. Blood pressure was recorded by a cannula in either the right carotid artery or one of the femoral arteries.

Dog 601.—With the dog under morphine and light ether anesthesia, the left carotid artery was exposed and freed from surrounding structures. Through an incision of half the circumference, the instrument for stretching was inserted into the arch and ascending aorta. The left femoral artery was also exposed, and a similar instrument was introduced into the abdominal aorta. Blood pressure was recorded by cannula in the right carotid artery. Repeated dilatation of the ascending aorta and arch failed to produce any material change in blood pressure. The passing of a dilator into the aortic ring produced a marked fall of blood pressure (64 mm. of mercury) immediately on dilation, which returned promptly to normal on removal of pressure. This was repeated a number of times. Dilation of the abdominal aorta repeatedly showed no effect on blood pressure, but following release of the last pressure there occurred a delayed rise in pressure of 44 mm. of mercury, which was maintained throughout the remainder of the experiment (fig. 11). Both vagi were severed, following which dilation of the ascending portion and arch produced no fall in blood pressure, but dilation of the ring produced a fall (48 mm. of mercury).

Before section of the vagi in this animal, the annulus of Vieussens was exposed and its connections with the vagus severed. During manipulation it was found that the blood pressure rose sharply, to fall with the cessation of mechanical stimulation. Repeated stimulation of the severed annulus of Vieussens and stimulation mechanically and electrically of the various branches to the cervical sympathetic produced a prompt definite rise in blood pressure (16 to 32 mm. of mercury) (fig. 12).

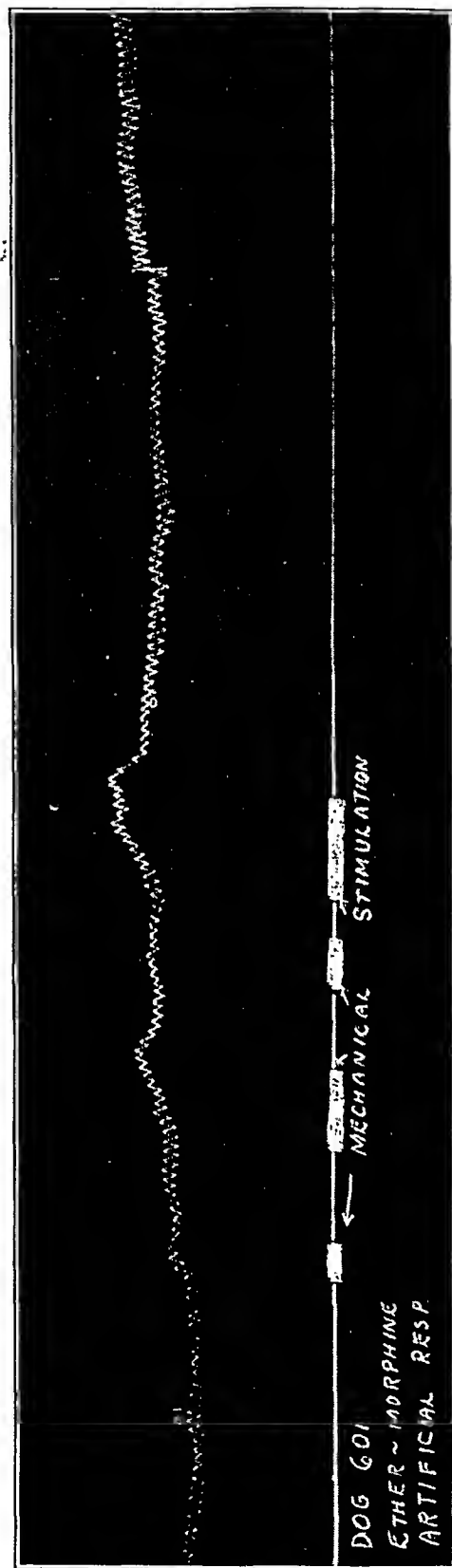
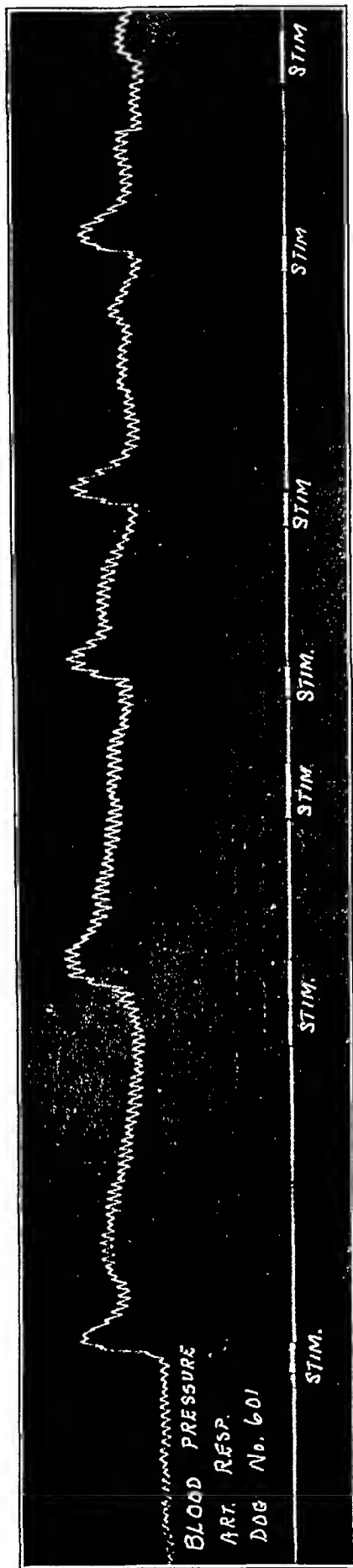


Figure 12

Fig. 12.—Curve for dog 601, showing the effect of electrical and mechanical stimulation of the annulus of Vieussens.

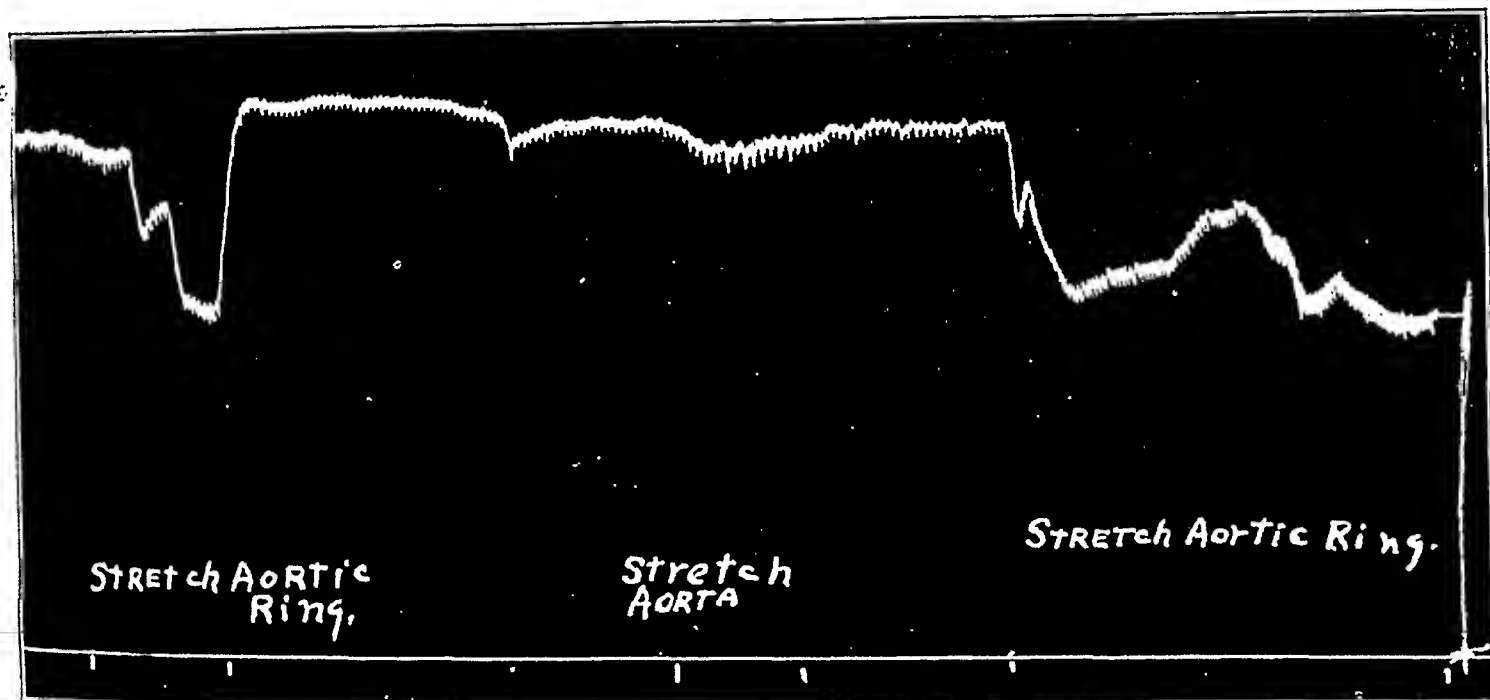
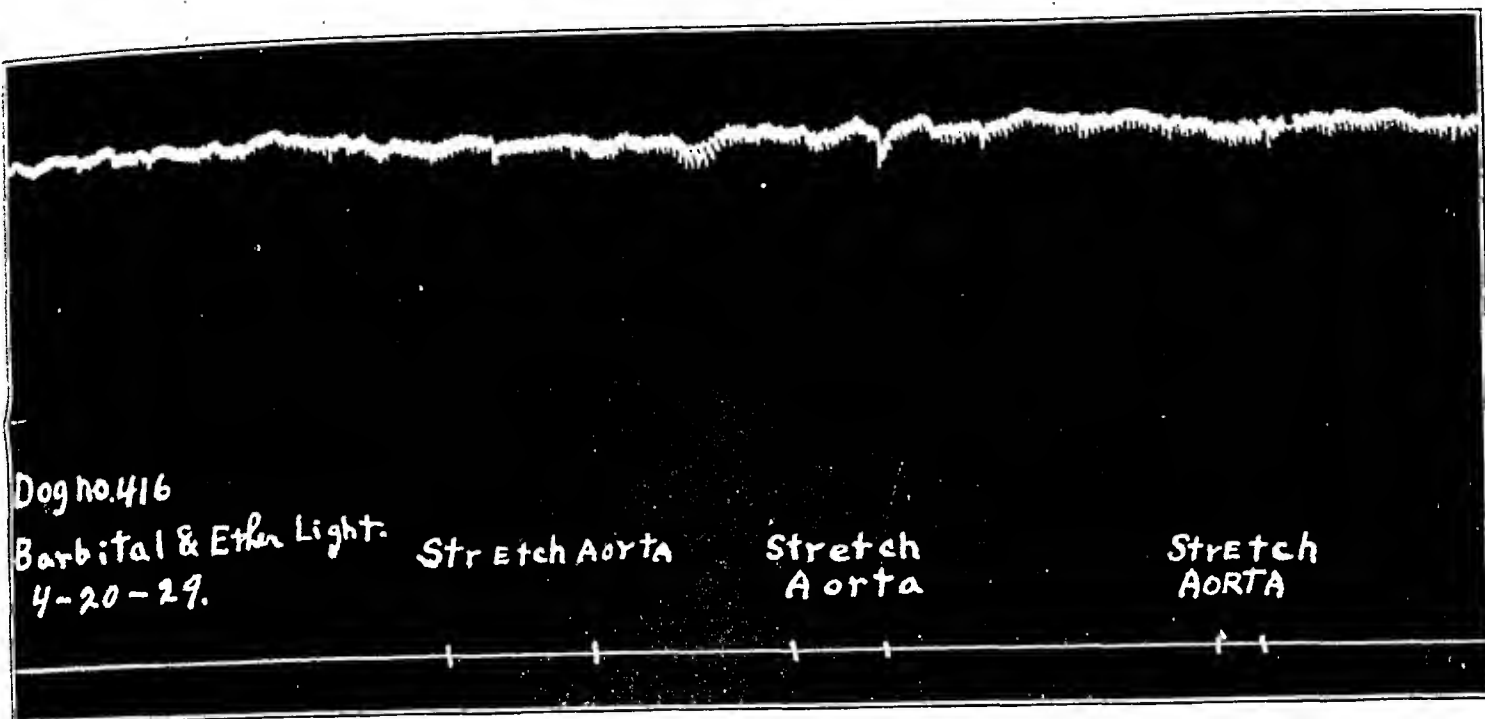


Fig. 13.—Curve for dog 416, showing absence of effect on blood pressure when aortic arch is stretched and marked effect when aortic ring is stretched (70 mm. mercury) at end; sudden death of dog occurred from blocking of coronary orifices.

Dog 416 A.—With the animal under light barbital anesthesia, the carotid artery was exposed and freed from the surrounding structures and incised for introduction of the dilator. The blood pressure was recorded by cannula in the right carotid. Stretching of the ascending portion of the aorta resulted in a slight fall of blood pressure (8 mm. of mercury). The instrument was passed on to the ring, but had stopped behind a cusp, and puncture of this cusp caused a fall in blood pressure (20 mm. of mercury). When the instrument was withdrawn and again passed into the ring (as recognized by its passing freely into the ventricle) and expanded, apparently the cusps were forced against the openings of the coronary artery, which produced immediate death (fig. 13). Dog 301 illustrates the effect of pressure on the posterior aortic cusps with a fall of blood pressure (42 mm. of mercury) (fig. 14).

Dog 418.—With the dog under barbital and light ether anesthesia, the carotid was exposed and the dilator introduced into the aorta. The blood pressure was

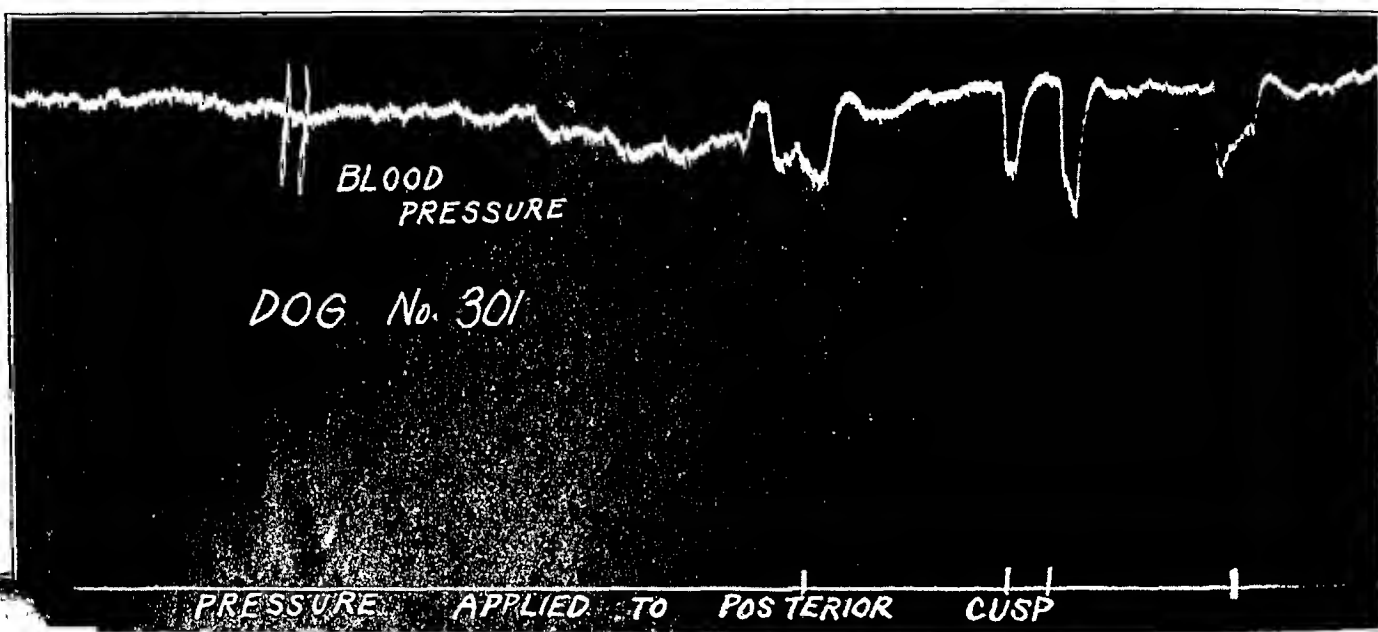


Fig. 14.—Effect on blood pressure of pressure applied to an aortic cusp.

recorded from the left femoral artery to eliminate the possibility that changes in the blood pressure might be due to interference in circulation of the carotid from which pressure had previously been taken. Repeated dilation of the arch and ascending aorta resulted in an increasing rise of blood pressure following each distention (8 to 26 mm. of mercury). When the instrument was passed into the ring and stretched, the coronary artery was accidentally blocked, resulting in sudden death (fig. 15).

Dog 414.—With the animal under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. Stretching of the arch and ascending aorta produced no change in pressure. Stretching of the aortic ring produced a fall in blood pressure (24 mm. of mercury). After severing of both vagi, stretching of the aortic ring produced a fall in blood pressure (fig. 16).

Dog 417.—With the dog under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by

cannula in the left femoral artery. Stretching of the aorta produced no change in blood pressure; stretching of the ring produced a fall (60 mm. of mercury). After severance of both vagi only a slight fall in blood pressure occurred as a result of dilating the ring (14 mm. of mercury).

Dog 416.—With the animal under barbital and light ether anesthesia, the carotid artery was isolated for introduction of the aortic dilator, blood pressure being recorded by cannula in the left femoral artery. Stretching of the ascending portion of the aorta and arch produced no fall in blood pressure. Stretching of the ring produced a fall (56 mm. of mercury). During another stretching of the ring, the coronaries were accidentally occluded, resulting in death.

Dog 415.—With the dog under light ether anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. Stretching of the ascending portion of

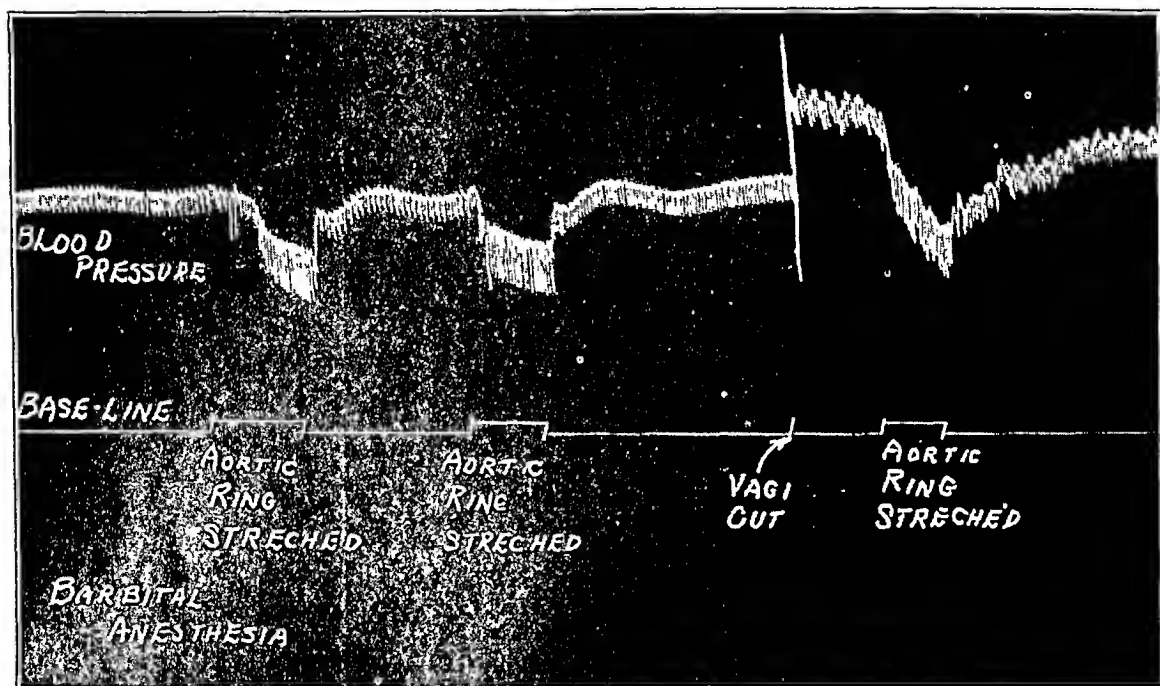


Fig. 16.—Curve for dog 414, showing effect of dilation of aortic ring and effect after severing the vagi.

the aorta and arch produced a rise (12 mm. of mercury) in blood pressure once. Later dilations had no effect. Stretching of the aortic ring produced a fall (40 mm. of mercury). Removal of the annulus of Vieussens and stretching of the ring produced a fall in pressure (58 mm. of mercury). Stretching of the arch produced a fall (8 mm. of mercury).

Dog 27.—With the animal under light barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded by cannula in the left femoral artery. On the first stretching of the aorta, one of the springs broke, producing a slight perforation of the arch of the aorta. This resulted in a marked rise in blood pressure (77 mm. of mercury) and great stimulation of respiration, followed by the rapid death of the animal (fig. 17).

Dog 32.—With the dog under barbital anesthesia, the carotid artery was isolated for introduction of the aortic dilator, the blood pressure being recorded

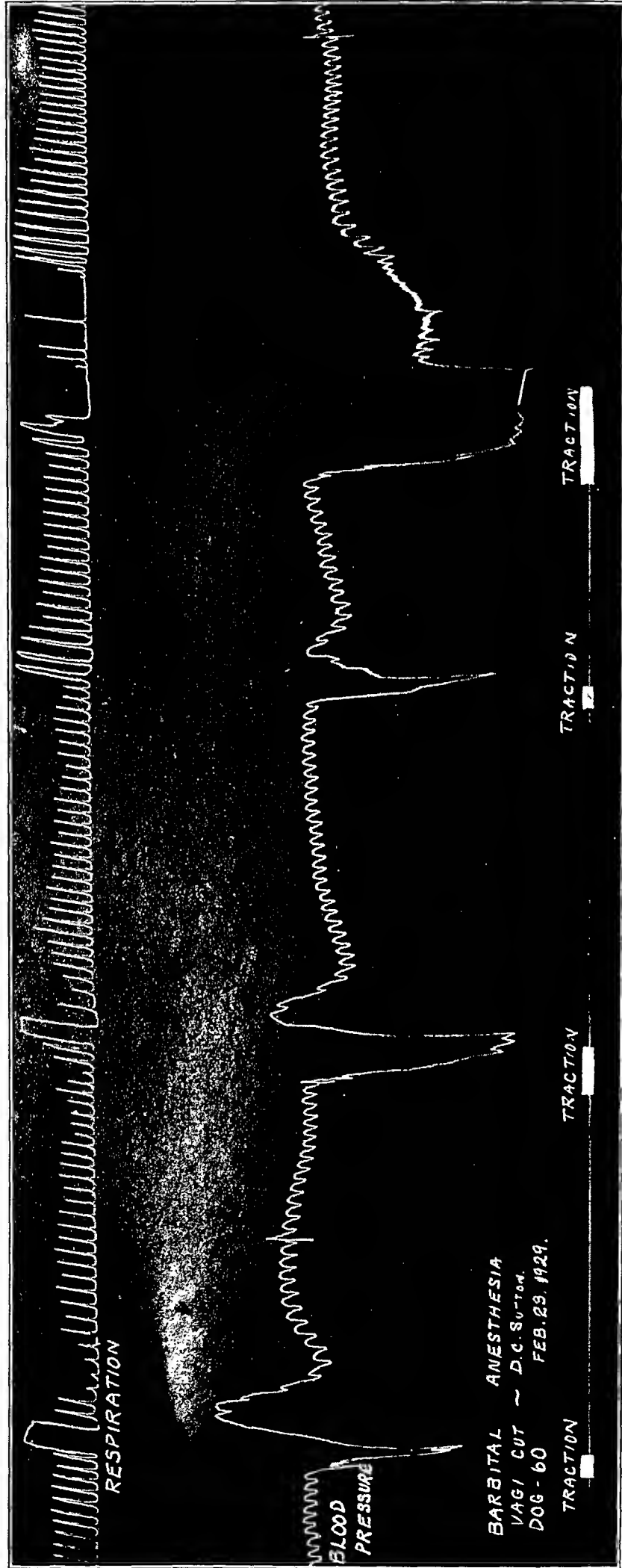


Fig. 19.—Curve for dog 60, showing effect of traction on the cordae tendineae. Continuous traction after section of the vagi and later the sympathetics caused death.

pressure. The reflex producing this rise in blood pressure is affected by anesthesia and by the variation in dogs.

As soon as this observation was made, a careful study of our clinical cases of aortitis, with and without aortic insufficiency, has shown hypertension above 150 mm. of mercury systolic pressure to be present in 40 per cent (thirty-four cases).

Dumas⁹ reported three cases of abdominal aortitis and one of thoracic aortitis in which there were paroxysms of hypertension, dyspnea and precordial pain. He explained these symptoms as being due to a functional constriction of some portion of the arterial system.

Stretching of the aortic ring produces a prompt fall in blood pressure which is proportional to the amount of tension. The fall in pressure occurs promptly and disappears just as promptly on release of tension. Section of both vagi and the left sympathetic has no constant appreciable effect, although in dog 417 severing both vagi resulted in a decrease in the fall. In dog 415 severance of the left sympathetic connections did not affect the fall. The evaluation of the mechanical effect on blood pressure of producing so great and sudden insufficiency of the aortic ring appears impossible.

Perforation of two cusps does not have so great an effect on the fall of blood pressure as does the distention of the aortic ring with the dilator. Pressure on a cusp (dog 301) probably does not cause a material aortic insufficiency, and yet produces a definite fall in blood pressure. It seems that the fall in pressure depends on a factor other than that of mechanical interference with normal blood flow, but further evidence is required to settle this point. This is also true of the fall in pressure on pulling on the chordae tendineae.

Stretching of the abdominal aorta in one experiment caused a rise in blood pressure.

Effects of Stimulation of the Annulus of Vieussens.—When the annulus of Vieussens was being severed, a marked rise in blood pressure was recorded. After severance of all connections with the vagus, repeated mechanical and electrical stimulation produced constant rises in blood pressure. Since this observation was made, Leriche and Fontaine¹⁰ have reported similar observations.

CONCLUSIONS

1. Acute mechanical distention of the aortic arch, ascending aorta, aortic ring and the cavity of the left ventricle does not produce pain in the dog.

9. Dumas, A.: Paroxysms of Hypertension and Pain in the Course of Aortitis, *J. de méd. de Lyon* 9:699 (Dec. 5) 1898.

10. Leriche, Rene, and Fontaine, Rene: Contribution to the "Physiology" of the Annulus of Vieussens, *Arch. d. mal. du cœur* 4:215 (April) 1929.

2. Acute mechanical distention of the parts of the aorta and heart named produces paroxysmal dyspnea.

3. Acute mechanical distention of the ascending aorta and aortic arch at times produces either a rise in blood pressure or no definite change.

4. Acute mechanical distention of the aortic ring of the left ventricle invariably produces a fall in pressure even when both vagi are severed.

5. Mechanical and electrical stimulation of the annulus of Vieussens after all vagal strands are severed invariably produces an increase in blood pressure.

6. According to the experimental evidence given in this paper, the only mechanism for the production of cardiac pain is that of lessened blood flow to the myocardium.

BUNDLE BRANCH BLOCK

THE PHENOMENON OF ITS DEVELOPMENT IN RELATION TO
AXIS DEVIATION OF THE HEART *

ALBERT S. HYMAN, M.D.

NEW YORK

AND

AARON E. PARSONNET, M.D.

NEWARK, N. J.

The difficulties experienced in differentiating between simple left axis deviation of the heart and beginning right bundle branch block are known to all clinicians interested in cardiovascular pathology. Observers of wide experience have noted from time to time that what appeared to be a simple left axis deviation of the heart at one electrocardiographic examination might subsequently and within a short time prove to be a true right bundle branch block.

During the past five years, we have observed a group of patients whose electrocardiograms showed certain common characteristics. In some of these patients complete right bundle branch block developed; in one of them, the condition started with what appeared to be a right axis deviation of the heart, and at death the electrocardiogram showed a left bundle branch disturbance.

A consideration of the earliest manifestations of bundle branch block forms the basis of this paper. The cases selected were chosen without regard to etiology or clinical diagnosis; they were taken solely because of the similarity of their tracings.

The subject of bundle branch block is not new; the experiments of Eppinger and Rothberger,¹ Eppinger and Stoerk,² Rothberger and Winterberg,³ and others have clarified the chain of events that brings about the characteristic electrodynamic disturbances of the heart which are now easily recognized as being associated with pathologic changes existing in the main branches of the conducting system. The accepted criteria of bundle branch block have been briefly outlined by Carter,⁴ Lewis⁵ and others. The principle characteristics may be stated as

* Submitted for publication, Nov. 8, 1929.

1. Eppinger and Rothberger: *Ztschr. f. klin. Med.* **70**:1, 1910.

2. Eppinger and Stoerk: *Ztschr. f. klin. Med.* **71**:157, 1910.

3. Rothberger and Winterberg: *Zentralbl. f. Herzkrankh.* **5**:206, 1913.

4. Carter, E. P.: Clinical Observations on Defective Condition in the Branches of the Auriculoventricular Bundle, *Arch. Int. Med.* **13**:803 (May) 1914.

5. Lewis, T.: *Heart* **4**:242, 1913.

follows: 1. A delay in the QRS complex occurs beyond 0.10 second. 2. The amplitude of the QRS complexes is usually increased. 3. The QRS complexes are notched, split or feathered. 4. The ventricular complex is generally diphasic; the QRS complex is in the opposite direction to the T wave. 5. The direction of the QRS complex in leads I and III determines the bundle branch which is involved.

Of these five characteristics, probably more attention has been devoted to the first than to any of the others. Before mere delay of transmission time of the QRS complex can be determined, the normal time relationship must be established. One finds no general agreement as to this figure; Lewis⁶ stated that from 0.03 to 0.04 is normal. Einthoven,⁷ in a comparative study, expressed the belief that 0.03 is the normal time in most mammalian hearts. On the other hand, Kraus and Nicolai expressed the opinion that 0.06 second is more common. Oppenheimer and Rothschild⁸ considered that these figures must be more flexible, and that transmission times as high as 0.1 second may be within normal limits. Wilson and Herrmann,⁹ in an exhaustive study, found that a delay of 0.1 second or over was the most important indication of the existence of a bundle branch disturbance. These authors have shown that the QRS complex may be modified in two ways: (1) by prolonging the time required by the excitation process to reach all parts of the ventricular muscle and (2) by changing the course of the excitation wave and thus also the order in which the various muscle regions pass into the active state.

Both these factors are important, for since the conducting systems of the two ventricles are not linked together except through the main stem of the bundle of His, the impulse can reach the ventricles affected by the lesion only by passing through the intraventricular septum and the adjacent muscular structures of the heart. The rate of the transmission of the impulse through such tissue is very slow. The point at which the impulse enters the Purkinje plexus of one or the other ventricle will determine to a considerable extent the order in which the various areas of the endocardial muscles of that ventricle are activated. In other words, the form and the duration of time exhibited by the QRS complex are apparently dependent on the new course assumed by the excitation wave as it passes through the ventricular muscle in order to complete its journey. Assuming that the QRS interval is

6. Lewis, T.: *Clinical Electrocardiography*, London, Shaw & Sons, 1924, vol. 3, p. 22.

7. Einthoven, W.: *Arch. f. d. ges. Physiol.* **149**:65, 1913.

8. Oppenheimer, B. S., and Rothschild, M. A.: *Electrocardiographic Changes Associated with Myocardial Involvement*, *J. A. M. A.* **69**:429 (Aug. 11) 1917.

9. Wilson, F. N., and Herrmann, G. R.: *Bundle Branch Block and Arborization Block*, *Arch. Int. Med.* **26**:153 (Aug.) 1920.

equal to the time during which the excitation wave is spreading plus the time required by the last muscle region activated to develop its full potential, it can be readily determined to what extent the first factor has been changed as the second is practically constant and of very brief duration (0.0085 second).

The course of the excitation wave as it spreads through the ventricles has been demonstrated by many observers. Entering the special conduction system of the ventricles by way of the bundle of His, it passes along the two chief branches of this structure and then frequently subdivides and terminates in the Purkinje system which lines the endocardial surface of both chambers. From the Purkinje plexus it spreads outward through the ventricular walls toward the epicardial surface of the heart. Wenckebach and Winterberg¹⁰ demonstrated with great accuracy the speed at which this impulse passes through the various portions of the heart; they have shown that the excitation process passes almost ten times as fast through the specialized pathway of conduction as through a new myocardial pathway.

There is still some discussion in regard to the continuity of the Purkinje system in the human heart; in the dog and the horse the system seems to be rather readily demonstrated, but there has never been a complete visualization of the entire system in man. Assuming, however, that the Purkinje fibers in the human heart resemble those of the laboratory animals, Lewis stated that in right bundle branch block the first part of the QRS complex is written by the spread of the excitation process in the left ventricle by way of the combined pathways of myocardium and Purkinje network; on the other hand, in left bundle branch block the QRS complex is written by a similar spread through the right ventricle.

Another factor concerned in prolongation of the QRS interval is unquestionably the retarded spread of the excitation wave through the intraventricular septum. Willius¹¹ has pointed out that the thickness of the septum may therefore have much to do with the delay in the transmission of the impulse; when the septum is very thick, as in greatly hypertrophied hearts, the delay is longer than in thinner septums uninvolved with such pathologic changes. In considering the relative frequency of right and left bundle branch block, many observers have suggested that the relative rarity of the latter condition is purely anatomic in origin, since the right main bundle is situated very superficially to the endocardium of the papillary muscles of the right side of the heart, and hence is more accessible to damaging proc-

10. Wenckebach and Winterberg: *Unregelmässige Herztätigkeit*, Leipzig, Wilhelm Engelmann, 1927, p. 87.

11. Willius, F. A.: *Am. Heart J.* 1:577, 1926.

evidence of a complete right bundle branch block. The QRS complex was now delayed to about 0.18 second; it was split and feathered, and the T wave in lead I was completely inverted. The patient died two weeks later during an acute attack of pulmonary edema.

CASE 2.—In a woman, aged 49, the previous cardiovascular history was essentially negative. One year prior to the first examination (fig. 2A) she began to complain of dyspnea and general weakness. She was seen by us for the first time at the age of 46; at that time, she showed a well marked left axial deviation of the heart with a diphasic T wave in the first lead and an upright T wave in the third lead. The QRS complex measured 0.06 second. There was a normal sinus rhythm. Both the heart and the aorta were somewhat enlarged; the blood pressure was 140 systolic and 90 diastolic. She was seen again about eight months later, when she was referred back to us because of an irregularity of the pulse. An examination at this time (fig. 2B) showed that the irregularity was due to a nodal extrasystolic arrhythmia. The QRS complexes had widened to 0.1 second

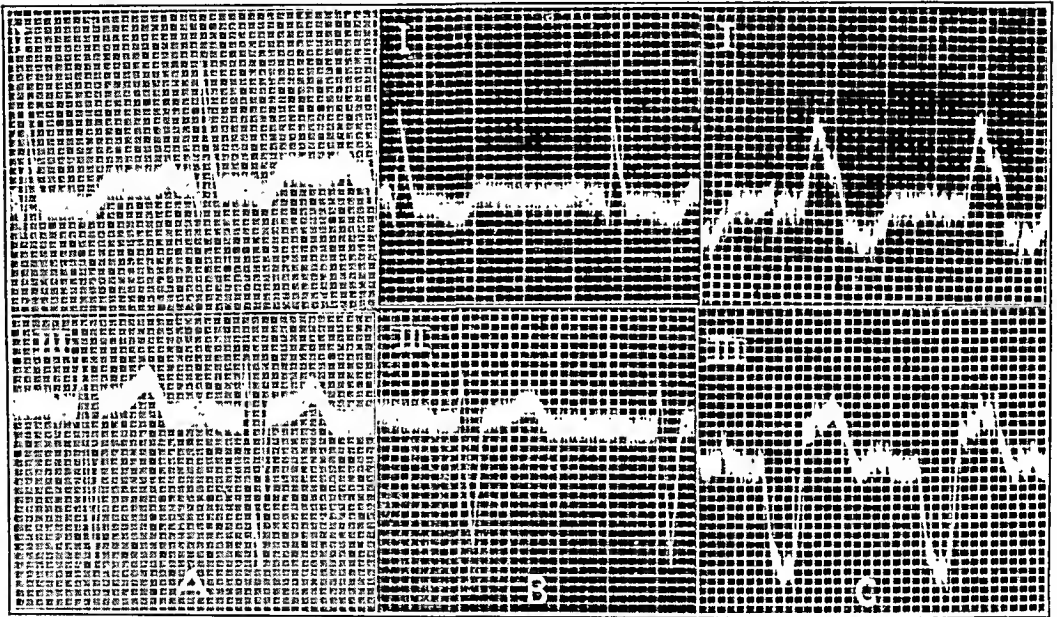


Fig. 1.—Typical development of pure right bundle branch block from a simple left axis deviation. Note the characteristic T wave alteration in lead I A.

and in the second limb of the complex both in the first and in the third leads; there were evidences of slurring. The T waves in the first lead had become more inverted, and those in the third lead more upright. She was seen again a year and a half later, this time with a well marked auricular fibrillation. The QRS complexes (fig. 2C) were now delayed to 0.12 second with notching, and the T waves were inverted in the first lead. The heart action became greatly decompensated, and the patient has been bedridden for the past year.

CASE 3.—A man, aged 62, had no previous cardiovascular history. He was beginning to complain of heart consciousness and palpitation, which were especially well marked after eating. He was being treated for gastro-intestinal symptoms when first seen. Electrocardiographic studies (fig. 3A) showed a well marked left axial deviation of the heart; the QRS complex was 0.08 second; the T wave in the first lead was definitely inverted, but in the third lead it was

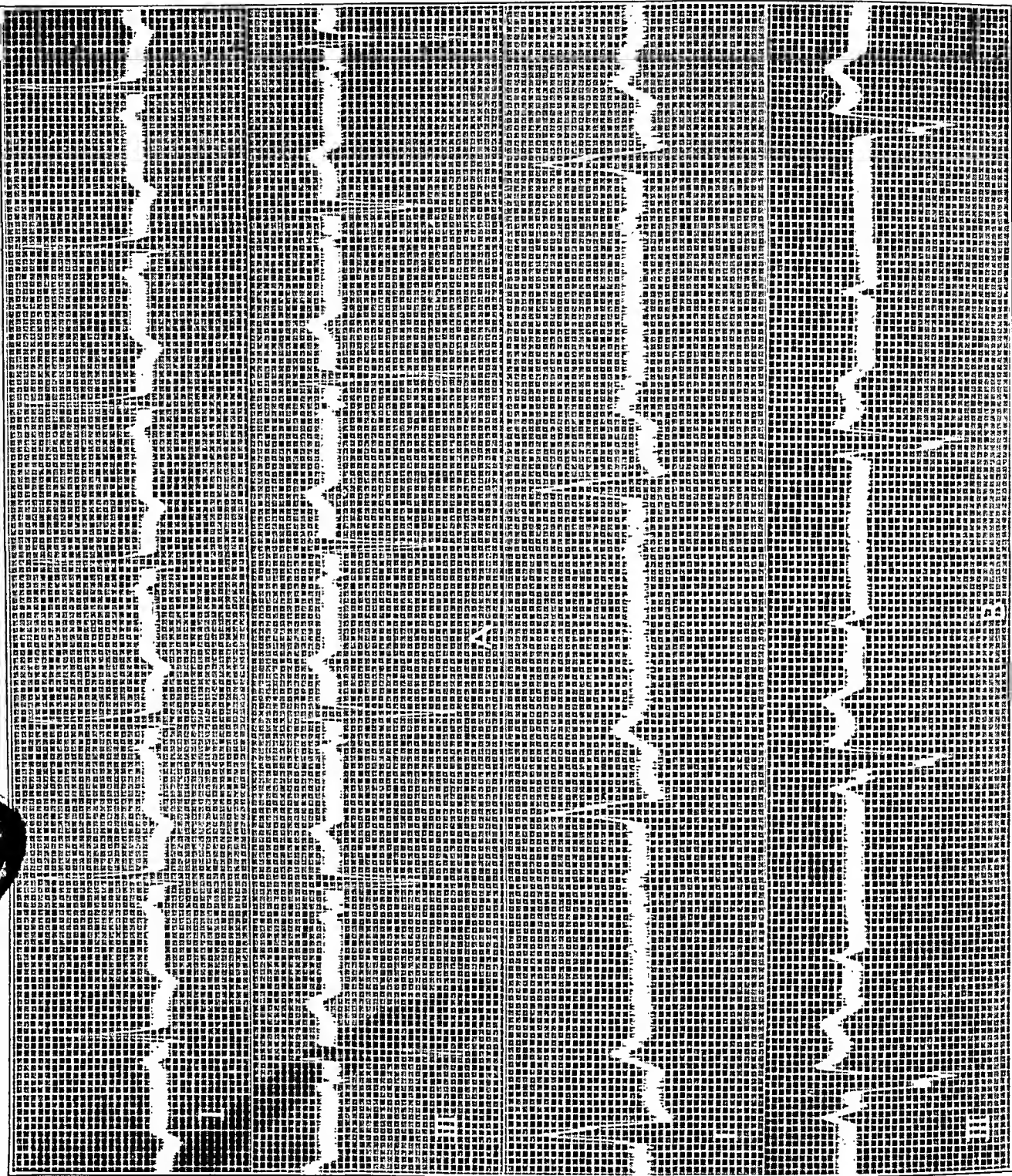


Fig. 3.—Complete auricular and ventricular dissociation with right bundle branch block developing two years after the discovery of an extreme left axis deviation.

upright. About two years later, the patient was again seen because of a slow and irregular pulse. Studies made at that time (fig. 3B) showed a complete auricular and ventricular dissociation; a complete right bundle branch block had also developed. The QRS complex was now delayed to 0.14 second, and the complexes were split and feathered. The T wave in the first lead while downward was somewhat altered because of the superimposed P waves. One year after this record was taken, the patient was still alive.

CASE 4.—A man, aged 54, had a previous history of cardiovascular disease dating from a severe attack of toxic nephritis which occurred four years before. The blood pressure was 190 systolic and 100 diastolic; both the heart and the aorta were enlarged. On the first examination (fig. 4A), a marked left axial deviation of the heart was noted. The QRS complex measured only 0.06 second; the T waves of the first lead were inverted and diphasic but were upright in the third lead. The patient was seen again about fourteen months later; his condition had slowly become worse and he was dyspneic, showing congestive signs of heart failure. He also had an irregular pulse. Electrocardiographic studies (fig. 4B) showed the full development of a right bundle branch block, the QRS complexes were delayed to 0.14 second, and the complex was split and feathered. The T waves in the first lead were markedly inverted while in the third lead they were upright. The irregularity noted in the pulse was found to be an extrasystole which was apparently coming from shifting foci in the right ventricle. The patient died about three days after the record was taken.

In this connection it may be useful and interesting to consider the process in cases in which the electrocardiogram shows a right instead of a left axis deviation of the heart. Such cases are extremely infrequent, and may be relatively as rare as the occurrence of left bundle branch block itself.

CASE 5.—A man, aged 56, had a long history of chronic bronchitis, emphysema and asthma. On physical examination, he showed the typical changes in the lungs seen in chronic pulmonary and bronchial disease, with associated cardiovascular changes. The heart, however, was not greatly enlarged, and blood pressure levels were maintained at 110 systolic and 70 diastolic. Electrocardiographic studies showed a right axial deviation of the heart; the QRS complex measured only 0.06 second; the T waves were upright in the first lead but inverted in the third. Because of his pulmonary condition, the patient was advised to live in the southwest; he stayed in Arizona for about three and a half years and returned, apparently much improved. Electrocardiographic studies (fig. 5B) showed a fully developed left bundle branch block with a delay in the QRS complex to about 0.14 second. There was apparently no other change in the cardiovascular system. After several attacks of pulmonary edema, the patient died suddenly.

The first four typical cases have been taken from a group of 46, all showing more or less similar electrocardiographic studies. This group represents a little more than 10 per cent of the total number of cases in which a left axis deviation of the heart was found in the course of a routine cardiovascular examination. We believe that 10 per cent is too high a figure to be merely coincidental, and we agree with the observations made by Luten and Grove that left axis deviation of the bundle branch block configuration must be considered in a

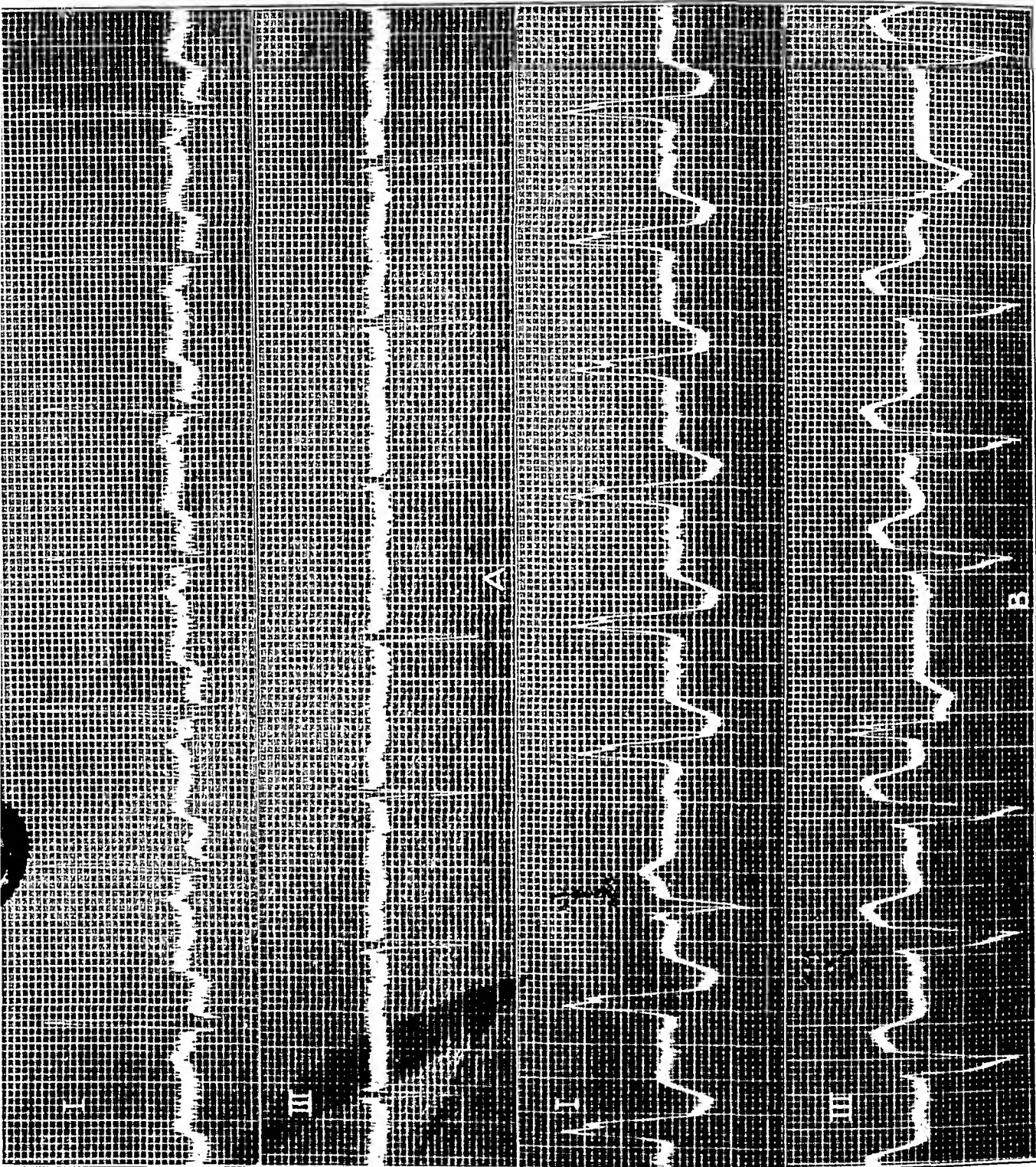


Fig. 4.—Well marked right bundle branch block with an extrasystolic arrhythmia developing fourteen months after the

coronary disease cannot be determined from electrocardiographic tracings unless changes in the T waves are found in two leads.

The relative rarity of left bundle branch block presents many interesting considerations. In case 5 we have seen a right axis deviation of the heart develop into a true left bundle branch block prior to a very sudden death. The configuration of the first tracing is theoretically what might be anticipated if the process by which right bundle branch block develops is true. The downward QRS complex and the upward T wave in the first lead and the upward QRS complex and downward T wave in the third lead are but the reverse picture of that found in right bundle branch disturbance.

SUMMARY

Left axis deviation of the heart is so frequently found in middle and advanced age periods that many observers regard such an electrocardiographic manifestation as normal. We have been impressed by the fact that more than 10 per cent of our series of left axis deviations have been associated with alterations in the T waves of the first and third leads which are suggestive of the bundle branch block configuration. In a follow-up study of these cases we have found that a right bundle branch block has developed in from eight months to four years. Such cases have terminated in pure right bundle branch block without change of sinus rhythm, bundle branch block with auricular fibrillation, bundle branch block with complete auricular and ventricular dissociation and bundle branch block with extrasystolic arrhythmia of single or multiple foci. The common etiologic origin of these four terminal stages may cause any one of them to be found with the others, and the step from one to another may be due to gradual extension of the degenerative process in the heart muscle.

Considerable prognostic information may thus be secured from close scrutiny of all electrocardiograms taken during the age periods mentioned. The onset of bundle branch block may sometimes be suspected, many months and even years prior to the actual development of the typical delayed conduction phenomena which are so characteristic of this condition.

METABOLISM AND TREATMENT OF OSTEOMALACIA

ITS RELATION TO RICKETS *

SAMUEL L. GARGILL, M.D.

DOROTHY ROURKE GILLIGAN, M.S.

AND

HERRMAN L. BLUMGART, M.D.

BOSTON

Although osteomalacia is a well recognized disease entity, complete metabolic studies using the newer nutritional methods are not available in the literature. An extremely advanced case of the disease recently observed by us over a period of one year offered an exceptional opportunity to study the disease and the effects of treatment.

HISTORICAL RÉSUMÉ

Pathology.—Various views have been held regarding the actual changes in the bones of patients with osteomalacia. Virchow¹ assumed that the inorganic part of bone was inert and without metabolism, and believed that osteomalacia was due to dissolution of the mineral constituents by an acid. Cohnheim² was the first to take exception to this view, asserting that even in adults, bones undergo active anabolism and catabolism. He believed that absorption of the organic and inorganic substances is accomplished in osteomalacia through the activity of the osteoclasts and that later new bone consisting of organic matrix free from lime salts is laid down. This concept of the nature of osteomalacia was strongly supported by the histologic studies of Pom-

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* The expenses of this investigation were aided in part by a grant from the DeLamar Mobile Research Fund of Harvard University.

* From the Thorndike Memorial Laboratory of the Boston City Hospital, the Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

1. Virchow, quoted by von Recklinghausen, F.: *Untersuchungen über Rachitis und Osteomalacie*, Jena, Gustav Fischer, 1910.

2. Cohnheim, J.: *Lectures on General Pathology*, translated by A. McKee, London, New Sydenham Society, 1889.

mer³ and Looser⁴ and by the chemical and metabolic studies of McCrudden.⁵ As a result of these studies, the condition is now generally considered to be the result of widespread softening and absorption of preexisting bone (haliteresis) and the formation of uncalcified new osteoid tissue.

Etiology.—While the studies of McCrudden demonstrate the nature of the pathologic changes in the bones in osteomalacia and the importance of pregnancy as a contributory factor, they do not throw light on the nature of the underlying causation. The more important etiologic theories concerning osteomalacia may be grouped under two headings: (1) Endocrine Abnormalities and (2) Vitamin Deficiency.

ENDOCRINE ABNORMALITIES

Parathyroid Dysfunction.—Certain authors have believed that osteomalacia results from dysfunction of the parathyroid glands because of their intimate relation to calcium metabolism. Some observers have considered that hyperparathyroidism leads to osteomalacia, while others have held hypoparathyroidism responsible. Erdheim⁶ as early as 1917 commented on the frequent occurrence of enlarged parathyroid glands in patients with osteomalacia and believed that the hypertrophy represented an inadequate attempt at compensation. The alteration of the parathyroid gland was thus considered a result and not a cause of the disease. Hoffheinz⁷ reported forty-five cases in which the patients had enlargement of one or more of the parathyroid glands. Of these patients, seventeen had osteitis fibrosa, eight had osteomalacia and two had rickets. Perretti,⁸ acting on the assumption that parathyroid deficiency

3. Pommer, G.: Untersuchungen über Osteomalacie und Rachitis, Leipzig, 1885.

4. Looser, E.: Ueber Spätrachitis und die Beziehungen zwischen Rachitis und Osteomalacie. Mitt. a. d. Grenzgeb. d. Med. u. Chir. **18**:678, 1907-1908; Ueber Spätrachitis und Osteomalacie; Klinische, röntgenologische, und pathologisch-anatomische Untersuchungen, Deutsche Ztschr.f.Chir. **152**:210, 1920.

5. McCrudden, F. H.: A Study of the Metabolism in Osteomalacia, Am. J. Physiol. **17**:211, 1906; The Composition of Bone in Osteomalacia, *ibid.* **17**:32, 1906-1907; The Effect of Castration on the Metabolism in Osteomalacia, *ibid.* **17**:211, 1906-1907; The Effect of Castration on the Metabolism, J. Biol. Chem. **7**:185, 1909-1910; Studies of Bone Metabolism, Especially the Pathological Process, Etiology and Treatment of Osteomalacia, Arch. Int. Med. **5**: 596 (June) 1910. McCrudden, F. H., and Fales, H.: Studies in Bone Metabolism: The Etiology of Non-Puerperal Osteomalacia, Arch. Int. Med. **9**:273 (March) 1912.

6. Erdheim, J., quoted by Biedl, A.: Innere Sekretion, ed. 2, Berlin, Urban & Schwarzenberg, 1913, p. 108.

7. Hoffheinz: Ueber Vergrößerungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern, Virchows Arch. f. path. Anat. **256**:705, 1925.

8. Perretti, V. R.: Il ricambio del calcio e gli estratti paratiroidi in un caso di osteomalacia, Riforma med. **43**:1062, 1927.

played an important rôle in the causation of osteomalacia, treated one patient with injections of a parathyroid extract and stated that it favorably affected the course of the disease.

Kerl⁹ reported one case of extreme osteomalacia in which the parathyroid glands were markedly hyperplastic, but suggested that the histologic changes in the glands might be secondary to the skeletal disease. No pathologic changes were found in any of the other endocrine glands.

Sauer¹⁰ suggested that undernutrition results in a suppression of the function of the parathyroid glands which, in turn, leads to a disturbance of lime salt metabolism resulting in malacia of the bones. Recently, Barr, Bulger and Dixon¹¹ demonstrated in man that hyperactivity of the parathyroid glands may be associated with decalcification of the skeleton, the clinical picture, however, being that of osteitis fibrosa cystica (von Recklinghausen's disease) rather than that of true osteomalacia. Similar cases have been reported by Wilder.¹²

Thyroid Dysfunction.—Morawiecka¹³ observed a patient with osteomalacia in whom a profound disturbance of the thyroid gland was evident, and Koeppen¹⁴ was likewise impressed by the relation between exophthalmic goiter and osteomalacia. These clinical observations are of interest in the light of the studies of Aub, Bauer, Heath and Ropes.¹⁵ They demonstrated that patients with exophthalmic goiter excrete abnormally large amounts of calcium and phosphorus and show rarefaction of bones on roentgen examination.

Thymus Dysfunction.—Scipiades¹⁶ reported an instance of osteomalacia which began during the patient's eighth pregnancy and progressed steadily for two years. The grafting of a thymus gland into

9. Kerl, F.: Zur Frage der Epithelkörperchenhyperplasien bei Osteomalazie und Osteoporose, Deutsche med. Wchnschr. **51**:1271, 1925; abstr., J. A. M. A. **85**:936 (Sept. 19) 1925.

10. Sauer: Hungerosteomalazie mit Tetanie, Deutsche med. Wchnschr. **45**:1373, 1919.

11. Barr, D. P.; Bulger, H. A., and Dixon, H. H.: Hyperparathyroidism, to be published.

12. Wilder, R. M.: Hyperparathyroidism: Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa, J. Endocrinol., to be published.

13. Morawiecka, J.: Un cas de maladie de Basedow associée à la sclérodermie et à l'ostéomalacie. Rev. neurol. **1**:217, 1928.

14. Koeppen: Ueber Knochenerkrankungen bei Morbus Basedowii, Neurol. Centralbl. **11**:219, 1892.

15. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism: III. The Effects of the Thyroid Hormone and Thyroid Disease, J. Clin. Investigation **7**:97, 1929.

16. Scipiades, E.: Erster durch Thymusimplantation geheilter Fall der Osteomalakie, Zentralbl. f. Gynäk. **48**:1885, 1924; abstr., J. A. M. A. **88**:1116 (April 12) 1924.

the abdominal wall of the patient resulted in the complete disappearance of the pains by the fourth day after operation. On the tenth day, the patient was able to walk. These clinical observations were made on the basis of experimental studies¹⁷ that indicated a close resemblance between osteomalacia and the osteoporosis following thy-mectomy in dogs.

Kloor¹⁸ described an extraordinary effect of the transplantation of a thymus gland from an infant, who had died of lobar pneumonia, into the rectus muscle of a 31 year old pregnant woman suffering from osteomalacia. Within seventeen hours of the transplantation, she gave birth to a normal female child. She improved rapidly, and left the hospital entirely symptom-free two weeks later.

Ovarian Dysfunction.—Fochier¹⁹ in 1879 removed the ovaries and uterus in a patient with osteomalacia. He reported remarkable improvement, and advised oophorectomy as a curative procedure. Fehling²⁰ in 1894 reported the first series of cases in which the patients were treated by this method, and claimed extraordinarily favorable results. Cristofolletti²¹ likewise ascribed the occurrence of osteomalacia to the abnormal persistence of ovarian function. McCrudden,⁵ however, was unable to subscribe to the opinions of these authors, and, after reviewing the literature critically, reported that only a small percentage of cases showed evidence of cure. McCrudden performed numerous experiments on animals, as well as a detailed study of a patient before, a few months after and a year following oophorectomy and noted no important changes in calcium metabolism. He also raised a pertinent question, saying "if osteomalacia is due to overactivity of the ovaries, it is difficult to understand how a patient without ovaries can have osteomalacia."

Cramer,²² however, in 1919 removed the ovaries of a pregnant woman with osteomalacia and reported that healing of the bones took

17. Scipiades, E.: Osteomalakiefälle, Zentralbl. f. Gynäk. **41**:953, 1917; Ueber Osteomalacie, Ztschr. f. Geburtsh. u. Gynäk. **81**:156, 1919.

18. Kloor, O.: Mit Thymus-Implantation behandelter Fall von Osteomalacie, Endokrinologie **2**:40, 1928.

19. Fochier, A.: Sur les modifications récentes de l'opération césarienne, à propos d'un cas d'amputation utéro-ovarienne comme complément de cette opération, Lyon méd. **31**:393, 473, 505 and 545, 1879.

20. Fehling, H.: Zehn Castrationen; Ein Beitrag zur Frage nach dem Werthe der Castration, Arch. f. Gynäk. **22**:441, 1884; Ueber Wesen und Behandlung der puerperalen Osteomalacie, ibid. **39**:171, 1891; Weitere Beiträge zur Lehre von der Osteomalacie, ibid. **48**:472, 1895; Ueber Osteomalacie, Ztschr. f. Geburtsch. u. Gynäk. **30**:471, 1894.

21. Cristofolletti, R.: Zur Pathogenese der Osteomalacie, Gynäk. Rundschau **5**:113 and 169, 1911.

22. Cramer: Zur Theorie und Therapie der Osteomalacie, Deutsche med. Wehnschr. **45**:475, 1919.

place with continuation of pregnancy. Gentili²³ ascribed the remarkable improvement in two patients with osteomalacia, one of whom had suffered for six years, to the oral administration of ovarian extract, although he also gave his patients calcium phosphate (amount not stated). Fraser²⁴ also maintained that osteomalacia is due primarily to ovarian hyperfunction.

Suprarenal Dysfunction.—Hoffmann²⁵ observed surprising clinical improvement following from five to ten hypodermic injections of epinephrine hydrochloride (1:1,000). Koltonski²⁶ was unable to alleviate his patient's condition by any treatment, including castration, until he injected epinephrine hydrochloride subcutaneously.

Edelmann²⁷ observed nineteen cases and stated that osteomalacia is related to a food deficiency and is precipitated in some persons by a pluriglandular disturbance. He injected epinephrine hydrochloride intramuscularly every three or four days, and believed that it caused the disappearance of pain and general clinical improvement.

Dayton²⁸ and Barrie,²⁹ on the other hand, observed no evidence of endocrine imbalance in the patients they studied. Similarly, Dock³⁰ found no evident endocrine abnormalities in sixteen cases, and Nadler³¹ stated "there is no real evidence that the frequent and manifold endocrine manifestations occurring in osteomalacia are a cause rather than an expression of the same metabolic disorder."

VITAMIN DEFICIENCY

Scott³² studied patients with osteomalacia in India, but was unable to discover any vitamin deficiency or other etiologic factor that might

23. Gentili, G.: Contributo clinico alla terapia e patogenesi dell'osteomalacia, *Riforma. med.* **38**:97, 1922; abstr., *J. A. M. A.* **78**:1427 (May 6) 1922.

24. Fraser, J. R.: The Ovary in Osteomalacia, *Am. J. Obst. & Gynec.* **14**:697, 1927.

25. Hoffmann, R.: Ueber eine gehäuft auftretende, deformierende Wirbelerkrankung und ihre Beziehungen zur Hunger-osteomalacie, *Wien. Arch. f. inn. Med.* **4**:91, 1922; abstr., *J. A. M. A.* **79**:1727, 1922.

26. Koltonski, H.: Ueber Osteomalacie, *Monatschr. f. Geburtsch. u. Gynäk.* **51**:253, 1920; abstr., *J. A. M. A.* **76**:1620 (Nov. 11) 1921.

27. Edelmann, A.: Ueber gehäuftes Auftreten von Osteomalacie und eines osteomalacieähnlichen Symptomenkomplexes, *Wien. klin. Wchnschr.* **32**:82, 1919.

28. Dayton, N. A.: Osteomalacia: Etiology and Report of a Case Occurring in an Imbecile with Psychosis, *Boston M. & S. J.* **188**:10, 1923.

29. Barrie, G.: Cancellous Bone Lesions, *Ann. Surg.* **61**:129, 1915.

30. Dock, G.: Osteomalacia, with a New Case, *Am. J. M. Sc.* **109**:499, 1895.

31. Nadler, W. H.: The Relation of the Endocrine Glands to Osteomalacia, *Endocrinology* **1**:40, 1917.

32. Scott, Agnes C.: A Contribution to the Study of Osteomalacia in India, *Indian J. M. Research* **4**:140, 1916; The Calcium Content of the Urine and Blood with Special Reference to Its Variation in the Condition of Osteomalacia, *ibid.* **4**:169, 1916.

be attributed to the diet. Hutchison and Stapleton,³³ on the basis of their experience in India, considered that osteomalacia and the type of rickets that occurs in adults are identical and that etiologic factors such as heredity, malaria, sanitation, early marriage and diet could be excluded. They pointed out that none of the great Indian famines was associated with late rickets or osteomalacia, although the food shortage was far greater than that in Vienna after the war. They considered lack of sunlight of greater importance, and pointed out that the seasonal incidence of "hunger malacia" in Vienna corresponded with seasonal changes in light, whereas there was no seasonal change in diet. They believed the lack of muscular activity in Indian women even more important than the lack of sunlight, especially since one patient became progressively worse in spite of daily exposure to sunlight.

Dalyell and Chick³⁴ reported that many patients in Vienna toward the end of 1918 complained of pains over the bones similar to that experienced in the early stages of osteomalacia. Marked improvement followed the administration of cod liver oil. No deformities of the bones were present in their subjects. Hume and Nirenstein³⁵ extended the studies of Dalyell and Chick and found that only 100 Gm. of cod liver oil was necessary to effect a marked clinical improvement. They believed that the disease was due primarily to a deficiency in fat-soluble vitamin. These authors stated, however, that they regarded the relation between hunger osteomalacia and the osteomalacia of pregnancy as quite uncertain.

Brenner³⁶ observed marked clinical improvement after the administration of phosphorus and cod liver oil to a patient with puerperal osteomalacia, and Higier³⁷ attributed the improvement in ten patients whom he treated similarly to the probable effect of vitamin A.

Miles and Feng³⁸ studied four cases of osteomalacia. Three of the patients received cod liver oil and improved, while one who received

33. Hutchison, H. S., and Stapleton, Grace: On Late Rickets and Osteomalacia, *Brit. J. Child. Dis.* **21**:96, 1924.

34. Dalyell, E. J., and Chick, H.: Hunger-Osteomalacia in Vienna, 1920: I. Its Relation to Diet, *Lancet* **2**:842, 1921.

35. Hume, E. M., and Nirenstein, E.: II. Comparative Treatment of Cases of Hunger-Osteomalacia in Vienna, 1920, as Out-Patients with Cod Liver Oil and Plant Oil, *Lancet* **2**:849, 1921.

36. Brenner, A.: Ueber Osteomalacie mit Epilepsy, *Deutsche Ztschr. f. Chir.* **176**:66, 1922; abstr., *J. A. M. A.* **80**:808, 1923.

37. Higier, H.: Endemie dysalimentärer Osteoarthropathie, Osteomalacie und Spätrachitis und ihre Stellung zur neuen Lehre von den Vitaminen oder Nutraminen, *Ztschr. f. klin. Med.* **500**:445, 1922; abstr., *J. A. M. A.* **80**:517 (March 17) 1923.

38. Miles, L. M., and Feng, C. T.: Calcium and Phosphorus Metabolism in Osteomalacia, *J. Exper. Med.* **41**:137, 1925.

olive oil did not improve. They performed excellent metabolic studies which indicated that osteomalacia as observed in China is a disease due to vitamin deficiency.

Goldstein³⁹ treated a male patient for severe osteomalacia with a vitamin preparation containing irradiated ergosterol; he also irradiated the patient with ultraviolet light and observed considerable clinical improvement. No studies of calcium and phosphorus metabolism were carried out.

Starlinger⁴⁰ observed conspicuous clinical improvement in a patient with osteomalacia following the administration of ergosterol.

It is evident from this brief résumé of the literature on osteomalacia that there are several forms of osteomalacia, and that the incidence, the clinical manifestations and the cause of the condition vary greatly in different parts of the world. The clinical and metabolic study of an American woman suffering from advanced and well defined osteomalacia herewith reported may be of assistance in the understanding of some of the problems concerning this disorder.

REPORT OF CASE

History.—Mrs. H. P., white, an American housewife, 38 years of age, was admitted to the Boston City Hospital on May 6, 1928, complaining of weakness, pains and tenderness over the bones and chest of two and a half years' duration.

There was no familial history of chronic bone disease, insanity, cancer, tuberculosis, diabetes or other disorder. Her father was killed in an accident at the age of 65. Her mother died at the age of 72, of an unknown cause. One brother was living and well; one was killed in the war. One sister died at the age of 17 of pneumonia.

It has been impossible to secure a complete marital history of the patient. She lived for some time in a remote city from which no report could be obtained. It is known, however, that she had had four alliances, which resulted in seven children, born twenty-four, twelve, eleven, ten, seven, five and two and a half years previous to her admission to the hospital. She had never had any miscarriages. She felt well throughout the pregnancies, had easy labors and was able to be up about the second day after delivery. Her last pregnancy, however, proved more difficult and marked the onset of her present illness. All living children were well, but the youngest child had evidences of rickets.

The patient slept well, getting an average of eight hours' sleep. Her household duties kept her rather confined to the house. She never took more than two cups of coffee and one cup of tea daily and was not addicted to alcohol or drugs. She ate red meat twice daily and a moderate amount of fresh green vegetables.

39. Goldstein, J.: Männliche Osteomalacie und Vigantol, Wien. klin. Wchnschr. 42:202, 1929.

40. Starlinger, W.: Ueber die Beeinflussung des Verlaufes einer schweren Osteomalacie durch bestrahltes Ergosterin, Deutsche med. Wchnschr. 53:1553, 1927.

She usually ate two apples and a pear every day, but did not like milk and took it rarely. She used little butter and never ate eggs or oranges. She usually ate cooked cereal once a day and average amounts of sugar, salt and condiments.

She never had severe headaches, vertigo or throbbing nor had she suffered injuries to her head. Her eyesight had always been good. She had never had any difficulty with her ears, nose or throat. Her teeth had never given her any trouble before her last pregnancy; then they caused considerable annoyance. Several loosened and fell out, while others developed large cavities and broke off. There had been no cardiorespiratory symptoms. Her appetite had always been good. Her bowels had always moved daily, and she never had been troubled with any gastro-intestinal symptoms. There had been no nocturia, frequency of urination or burning micturition. She had contracted syphilis twelve years previously and had received intensive treatment. Her Wassermann reaction, ten years previously, had been negative. Catamenia had begun when she was 8 years of age, had always followed a thirty-day cycle and was not associated with pain. The flow, which was not excessive, lasted from four to five days. Her last catamenia was one week before admission.

There had been no fainting spells, muscular twitchings or paresthesias. Her memory was good.

Her best weight had been about 135 pounds (61.2 Kg.), four years previously. On admission to the hospital, she weighed 86½ pounds (39.2 Kg.).

Present Illness.—The patient dated the onset for her present illness from the birth of a full time baby on Jan. 26, 1926, two and a half years before admission, although, as stated, she had felt far from well during the entire course of her pregnancy, experiencing generalized pains and aches, particularly during the final months. The birth was precipitous, but she did not lose much blood. On the third day after delivery, she left bed, against the advice of her physician and district nurse, and noticed that she failed to "pick up" as quickly as after previous pregnancies. She felt extremely weak, and on attempting to do her housework was forced to rest every few minutes. She continued, however, to nurse the baby.

Two years before admission, she noticed pain and a tight feeling around the left hip. A swelling then appeared in that region, which gradually increased in size and finally involved the lower part of the abdomen. A physician whom she consulted said that she had a "false pregnancy," but her periods remained perfectly regular. After seven months or seventeen months before admission, the swelling began to diminish and finally disappeared. She then felt fairly well for about a month. Generalized pains and aches returned, however, and for the next nine months she was unable to attend to her household duties on account of weakness and increasing discomfort. Seven months before admission, while putting one of her children to bed, she suddenly felt numb all over and moved with difficulty. Her left side felt especially weak, and she was unable to move the left eyeball. Her physician said that she had had a shock and ordered her to bed for three weeks. At the end of this time, she felt a little better, but was extremely weak. Six months before admission, she noticed that she was becoming shorter and that her back was humped. On her own initiative, she began to take 1 tablespoonful of fresh, unrefined cod liver oil twice a day, on alternate days. She became progressively weaker and was finally unable to leave bed. All her bones ached so much that she was unable to remain in one position for any significant length of time. Three months before admission to the hospital, she developed excruciating pain in the left side of the chest. The ribs on that side

seemed to her to have caved in and were so tender that she could not touch herself or lean back in bed without its causing great pain. Her chest felt tight and narrow, and excruciating pains appeared in both shoulders, legs and spine. Because of her extreme helplessness and the excruciating pain, she was forced to enter the hospital.

Physical Examination.—The patient was a deformed, extremely emaciated, young, white woman, lying in bed, mentally clear, but evidently in great pain. The skin was a dull, pasty white. The head was symmetrical, with no exostoses or depressions. The scalp showed no scars, but was tender over the occipital region. The hair was dark, plentiful and of normal texture. The eyes seemed prominent because of the emaciation of the face. The sclerae were strikingly blue; the conjunctivae, pale. The pupils were equal and regular, and reacted actively to light and accommodation. There was no exophthalmos, nystagmus or lid-lag. Joffroy's sign was negative. There was no ptosis. The extra-ocular movements were normal. By finger tests, the visual fields showed no gross abnormalities. Ophthalmoscopic examination showed pale fundi, no fresh or old hemorrhages, normal vessels and clearly outlined disks. The ears presented no deformity or discharge, and the drums appeared normal. The nose showed no discharge or obstruction. The lips were dry and slightly bluish. The mucous membranes were pale. The teeth were grayish rather than white and showed extensive necrosis and caries. Many were loose and showed large cavities. There was extensive pyorrhea of the gums, especially anteriorly. The tongue was smooth, shiny and slightly atrophic, and protruded in the midline without tremor. The throat was clear. The thyroid was palpable and prominent, but no thrill or bruit was present. There was no adenopathy. The thorax was conspicuously deformed and asymmetrical, showing marked flaring of the costal margins and an extensive depression in the left side of the chest, extending from the left axilla anteriorly to the midclavicular line. There was a thoracic scoliosis on the left and compensatory lordosis of the lower thoracic and lumbar vertebrae. The ribs could not be felt over the depression in the left anterior side of the chest. Palpation of the thorax was generally unsatisfactory because of the exquisite tenderness. The respiratory expansion was markedly limited. Laterally, the lower costal margins almost touched the iliac crests. The cardiac impulse was forceful and was seen and felt in the fifth left interspace, 7.5 cm. from the midsternal line. The right border of dullness was not made out because of the tenderness. The heart sounds were of good quality, and there was a soft systolic murmur at the apex. The rate was 90, and the rhythm was regular. Neither the arteries nor the veins showed sclerosis. The radial pulses were equal and regular; the rate, 88. The blood pressure was 110 mm. of mercury systolic and 70 diastolic. The lungs were clear and resonant throughout, except at the right lower part of the back, where the breath sounds were harsher than normal. The abdomen was level and the abdominal wall was extremely thin and atrophied, showing many transverse folds when the patient sat or stood up. There was no tenderness or spasm. No masses were felt, and the liver, spleen and kidneys were not palpable. The iliac crests were exceedingly prominent, especially on the right. The symphysis pubis was prominent, "beaked" and exquisitely tender. The results of the rectal examination were negative. A gynecologic consultant reported, "Multiparous introitus, moderately relaxed pelvic floor, and bilaterally scarred cervix. Uterus in good position and normal in size. Vaults negative. Marked tenderness of symphysis pubis." Both upper and lower extremities showed marked atrophy of the soft tissues and exquisite tenderness on pressure. There were no apparent fractures. The left thigh and leg were tender and pain-

ful, particularly on motion. No edema, varicosities, deformities or clubbing were present. The superficial reflexes were normal, while the knee and ankle jerks were increased. There were no Kernig, Babinski, Trousseau or Chvostek signs. There was no ataxia, except that the left arm moved somewhat unsteadily and jerkily in the finger to nose test. The position sense was good. There was a moderate scoliosis and lordosis of the thoracic spine. The patient weighed 86½ pounds (39.2 Kg.) and was 59¼ inches (150.6 cm.) in height.

Clinical Pathologic Examination.—The hemoglobin was 60 per cent (New-comer). The red blood cell count was 3,500,000, and the white blood cell count, 8,000 per cubic millimeter. The differential white blood cell count per hundred cells was: polymorphonuclear neutrophils, 60; polymorphonuclear eosinophils, 2; lymphocytes, 35; monocytes, 3. The red blood cells were slightly but definitely achromic and showed slight poikilocytosis and anisocytosis. The reticulocytes were sparse. The icteric index was 4. The Kahn and Wassermann reactions of the blood were negative on four successive examinations. The urine was normal. The basal metabolic rate was +6 per cent.

Roentgenologic Examination.—The roentgenologic examination by Dr. Max Ritvo showed a "marked degree of lime absorption with diminished density of all the bones and marked thinning of the cortex. There is a marked scoliosis to the left in the dorsal region. The ribs on the right side are collapsed, angulated, and the interspaces are very markedly narrowed. The epiphyses of the long bones show the same degree of lime absorption and thinning of the cortex. The findings are consistent with osteomalacia."

Diagnosis.—On the basis of the history, physical appearances and roentgenologic studies, a diagnosis of osteomalacia was made. On the advice of Dr. George R. Minot, the patient was transferred to a special ward for study and treatment.

METHOD OF STUDY

Changes in calcium metabolism occur so slowly that it was thought the patient would hardly survive a sufficient length of time to allow prolonged periods of clinical observation after offering various therapeutic agents. It was important, accordingly, to place the patient under strict metabolic observation so that the effect of treatment could be learned after comparatively few days of study. In addition to studies of the calcium, phosphorus and nitrogen metabolism, pertinent chemical examinations of blood and spinal fluid were made. X-ray pictures were taken of the entire skeleton of the patient under standard conditions, and complete measurements of the body were made at the beginning of treatment and at appropriate subsequent intervals. The first objective was to learn the endogenous calcium and phosphorus metabolism of the patient. As pointed out by Bauer, Albright and Aub,⁴¹ the factors that influence calcium metabolism are many and must be kept constant if the comparative effects of different therapeutic agents are to be studied. We are indebted to Dr. Joseph C. Aub, Miss Constance Fulton and Miss Helen Heywood for their cooperation. Through the cooperation of Dr. Aub, it was possible to establish the proper routine and precautions as outlined in the following paragraphs.

41. Bauer, W.; Albright, F., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: II. The Calcium Excretions of Normal Individuals on a Low Calcium Diet, Also Data on a Case of Pregnancy, *J. Clin. Investigation* 7:75, 1929.

TABLE 2.—*Diet 2. Diet 1, Plus 250 Cc. Boiled Skimmed Milk Daily*

	Break- fast, Gm.	Din- ner, Gm.	Sup- per, Gm.	Total Gm.	Carbohy- drate, Gm.	Pro- tein, Gm.	Fat, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.
Skimmed milk.....	125	...	125	250	12.75	8.5	0.75	0.305	0.210
Salt, 3 Gm.									
Total grams, diet 1.....					256.41	49.37	57.25	0.095	0.591
Total grams, diet 2 (calories, 1,839).....					269.16	57.87	58.00	0.400	0.831

TABLE 3.—*Diet 3. High Vitamin, High Calcium and Phosphorus*

	Break- fast, Gm.	Din- ner, Gm.	Sup- per, Gm.	Total Gm.	Carbohy- drate, Gm.	Pro- tein, Gm.	Fat, Gm.	Cal- cium, Gm.	Phos- phorus, Gm.
Orange juice.....	75	75	8.1	0.022	0.013
Eggs.....	50	...	50	100	13.40	10.5	0.067	0.180
Oatmeal.....	20	20	13.5	3.20	1.4	0.014	0.078
Bread.....	50	50	50	150	79.5	15.90	4.2	0.081	0.132
Butter.....	20	20	20	60	0.60	51.0	0.009	0.009
Milk (whole).....	200	...	200	400	20.0	12.20	16.0	0.480	0.372
Cream, 20 per cent.....	50	50	2.3	1.30	9.3	0.043	0.034
Sugar.....	20	10	...	30	30.0
Potato.....	...	100	...	100	20.0	1.90	0.1	0.011	0.048
Carrots.....	...	100	...	100	9.3	1.10	0.4	0.056	0.046
Steak.....	...	75	...	75	15.95	6.0	0.006	0.129
Ice cream.....	...	200	...	200	40.8	4.10	30.8	0.143	0.112
Lettuce.....	20	20	0.6	0.24	0.1	0.009	0.008
Olive oil.....	10	10	10.0
Lemon juice.....	10	10	1.0	0.002	0.001
Tomatoes (fresh).....	100	100	4.0	1.20	0.2	0.007	0.055
Peaches (fresh).....	100	100	9.4	0.70	0.1	0.016	0.024
Salt, 3 Gm.									
Total grams (total calories, 2,507).....					238.5	72.79	140.2	0.967	1.241

TABLE 4.—*Plan of Diet and Medication*

Period	Diet	Medication
1, 2	1	Control periods, with no medication; low calcium and low vitamin
3, 4	2	No medication; sufficient calcium, low vitamin
5, 6	2	50 cc. cod liver oil daily, given with meals
7, 8	2	50 cc. cod liver oil, and 18 oscodal tablets daily, 6 at each meal
9, 10, 11, 12, 13	2	50 cc. cod liver oil, 18 oscodal tablets and ultraviolet irradiation* from a mercury quartz lamp, daily
14, 15	1	Control periods, with no medication; low calcium, low vitamin
16, 17, 18	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light, daily; in addition, 1.24 Gm. calcium as calcium lactate daily with meals
19, 20	1	Control periods with no medication; low calcium, low vitamin
21, 22, 23, 24	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light; in addition, 3 Gm. phosphorus, as disodium acid phosphate daily with meals
25, 26	1	Control periods with no medication; low calcium, low vitamin
27, 28, 29	2	50 cc. cod liver oil, 18 oscodal tablets, ultraviolet light; in addition, 1.24 Gm. calcium as calcium lactate and 3 Gm. phosphorus as disodium acid phosphate daily with meals
30, 31, 32, 33	3	Diet rich in native vitamins, calcium and phosphorus; cod liver oil, oscodal and ultraviolet light as above; calcium as calcium lactate and phosphorus as disodium acid phosphate added to make calcium and phosphorus intake same as in periods 27, 28 and 29

* The ultraviolet irradiation was given by means of an air-cooled mercury quartz lamp. At the beginning, the patient was exposed front and back for two minutes at a distance of 20 inches (50.8 cm.). This distance was decreased and the time of exposure increased in accordance with the reaction of the patient, so that at the end of the period of observation she was exposed for twenty minutes, at a distance of 6 inches (15.24 cm.).

milk to the diet (diet 2). Although the patient received amounts greatly in excess of the normal metabolic requirement, she continued in negative calcium and phosphorus balance. Fifty cubic centimeters of a physiologically tested preparation of cod liver oil, an amount much greater than that considered adequate by other investigators, was then added to her diet (periods 5 and 6), but no appreciable storage of calcium or phosphorus resulted. Since patients with pernicious anemia who take small amounts of liver (40 Gm. daily) usually experience no improvement in contrast with the rapid and striking improvement when adequate large amounts are taken,⁴⁷ it was thought that if our patient took much larger doses of cod liver oil it would be beneficial, although she had taken supposedly adequate amounts of cod liver oil both before and since entering the hospital. The properties of cod liver oil made this impossible, so a physiologically tested concentrate in tablet form was administered instead.⁴⁸ Eighteen tablets (the vitamin A equivalent of 180 cc. and the vitamin D equivalent of 38 cc. of cod liver oil, were given daily in addition to 50 cc. of cod liver oil. As shown in table 5, the patient was able for the first time to store appreciable amounts of calcium and phosphorus (periods 7 and 8). In periods 9 and 10 (table 5), ultraviolet light irradiation was added to the regimen. Conspicuous improvement in the patient's general condition was evident. The tenderness of the bones had disappeared, except over the pubis, and the patient felt stronger. The results were so gratifying, both clinically and from the standpoint of calcium and phosphorus retention, that the same therapeutic measures were continued for three more periods (11, 12 and 13) (table 5).

The patient was now definitely in positive calcium and phosphorus balance, but we believed that the retention might be further increased by giving larger amounts of the bone-forming elements. In order to learn the relative importance of calcium and phosphorus, each was increased separately. Later, both were given together in large amounts. In periods 16, 17 and 18, 1.24 Gm. of calcium in the form of chemically pure calcium lactate was added daily to the regimen of periods 9 to 13. Calcium lactate was used, because it is a neutral salt and is

47. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**:470 (Aug. 14) 1926.

48. Oscodal (Metz), a preparation of the nonsaponifiable fraction of cod liver oil, containing the antiophthalmic and antirachitic fat-soluble vitamins. It has 500 times the antiophthalmic (vitamin A) potency of cod liver oil when assayed by the method of the United States Pharmacopeia for cod liver oil, and its antirachitic (vitamin D) potency is such that 0.0002 Gm. of oscodal (equivalent in potency to 0.02 Gm. of the oil) per day will suffice to initiate recalcification in the leg bones of young albino rats in ten days. Each coated tablet contains 0.02 Gm. of oscodal.

readily absorbed.⁴⁹ The daily amount was divided into three doses and given with the meals, so that the salt would be in the stomach and upper intestine when the environment was most acid and therefore most favorable for maximum absorption. As shown in table 5 and "block" G of figure 1, the retention of calcium was tripled and that of phosphorus significantly increased. Further analysis of these data will be given subsequently in this paper.

In order to demarcate the results, no medication was given in periods 19 and 20, and then 3 Gm. of phosphorus in the form of dis-

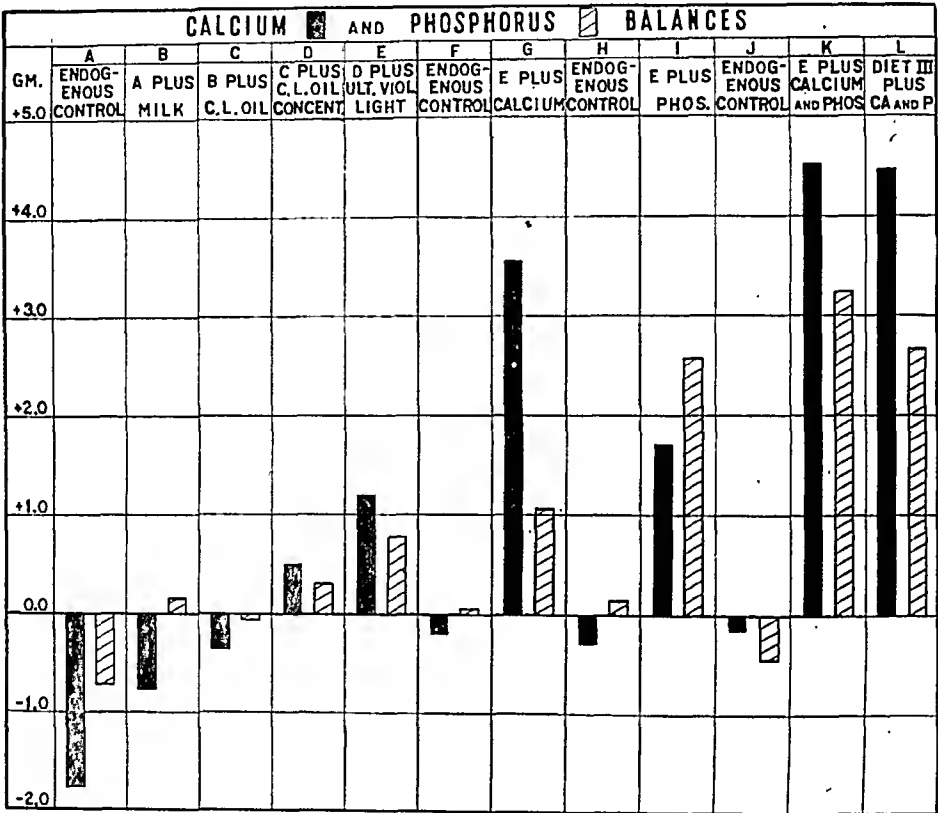


Fig. 1.—Calcium and phosphorus balances of patient with osteomalacia. The solid columns represent the actual calcium balance. The hatched columns represent the phosphorus balance obtained by subtracting the theoretical phosphorus combined with body protein from the actual phosphorus balance. Each section, lettered A to L, represents the average results of two or more consecutive three-day periods obtained on the regimen described briefly on the figure and in detail in the text.

odium acid phosphate was added daily to the diet and treatment as given in periods 9 to 13. Disodium acid phosphate was used because it is the most neutral of the sodium phosphate salts. It was given in three doses with meals, as was the calcium lactate.

49. Bauer, W., and Ropes, M. W.: The Effect of Calcium Lactate Ingestion on Serum Calcium, *J. A. M. A.* **87**:1902 (Dec. 4) 1926.

employed here is that used by Albright, Bauer, Ropes and Aub.⁴⁶ The results show that actual and calculated phosphorus balances agree closely during both the period of negative and that of positive calcium balances. This demonstrates that measurement of the calcium and phos-

TABLE 6.—*Comparison of Actual and Calculated Phosphorus Balances*

Period	Phosphorus Balances					Phosphorus Intake, Gm.
	Theoretical, Calculated from Calcium Balance, Gm.	Theoretical, Calculated from Nitrogen Balance, Gm.	Total, Theoretical, Gm.	Actual, Gm.	Difference, Actual Minus Calculated, Gm.	
1.....	-0.86	+0.12	-0.74	-0.70	+0.04	1.83
2.....	-0.75	+0.03	-0.72	-0.57	+0.15	1.83
3.....	-0.29	-0.25	-0.54	-0.04	+0.50	2.55
4.....	-0.39	+0.14	-0.25	+0.23	+0.48	2.55
5.....	-0.38	+0.15	-0.23	-0.12	+0.11	2.55
6.....	+0.05	+0.20	+0.25	+0.34	+0.09	2.55
7.....	+0.16	+0.26	+0.42	+0.32	-0.10	2.55
8.....	+0.28	+0.03	+0.31	+0.55	+0.24	2.55
9.....	+0.48	+0.21	+0.69	+1.02	+0.33	2.55
10.....	+0.50	+0.23	+0.73	+1.05	+0.32	2.55
11.....	+0.49	+0.20	+0.69	+0.94	+0.25	2.55
12.....	+0.66	+0.31	+0.97	+1.24	+0.27	2.55
13.....	+0.56	+0.20	+0.76	+0.89	+0.13	2.55
14.....	-0.03	+0.16	+0.03	+0.25	+0.17	1.83
15.....	-0.09	+0.18	+0.09	+0.18	+0.09	1.83
16.....	+1.73	+0.70	+2.43	+1.57	-0.86	2.55
17.....	+1.11	+0.67	+1.78	+1.64	-0.14	2.55
18.....	+1.94	+0.54	+2.48	+1.90	-0.58	2.55
19.....	-0.28	+0.29	+0.01	+0.37	+0.36	1.83
20.....	+0.01	+0.22	+0.23	+0.42	+0.19	1.83
21.....	+0.75	+0.14	+0.89	+3.79	+2.90	9.00
22.....	+0.79	+0.06	+0.85	+2.66	+1.81	9.00
23.....	+0.73	+0.25	+0.98	+1.75	+0.77	9.00
24.....	+0.76	+0.32	+1.08	+2.80	+1.72	9.00
25.....	-0.07	+0.25	+0.18	-0.43	-0.61	1.83
26.....	-0.06	+0.35	+0.29	+0.15	-0.14	1.83
27.....	+1.92	+0.39	+2.31	+3.92	+1.61	9.00
28.....	+2.01	+0.47	+2.48	+3.56	+1.08	9.00
29.....	+2.14	+0.37	+2.51	+3.48	+0.97	9.00
30*.....	+1.72	+0.59	+2.31	+2.89	+0.58	9.00
31*.....	+1.72	+0.59	+2.31	+2.89	+0.58	9.00
32*.....	+2.28	+0.56	+2.84	+3.57	+0.73	9.41
33*.....	+2.28	+0.56	+2.84	+3.57	+0.73	9.41

* The results of periods 30 and 31 were obtained by dividing one six-day period by 2 for the purpose of comparison. The results of periods 32 and 33 were obtained similarly.

phorus balances as accomplished in this study affords a direct approach to the study of the metabolism of bone.

In view of the close correspondence in most of the periods, the occasional discrepancies are of considerable interest. In periods 16, 17 and 18 (table 6), in which the calcium intake was increased without a corresponding increase in phosphorus, more phosphorus was excreted than theoretically expected. It may seem curious that all of the small

a slight secondary anemia at the beginning of treatment, but this vanished by the time of the last observations. The white blood cell count was repeated at frequent intervals during these months and ranged from 4,000 to 7,000 per cubic millimeter. The carbon dioxide combining power of the serum was 56.6 per cent by volume; the nonprotein nitrogen of the blood was .26 mg., and the blood sugar 94 mg. per hundred cubic centimeters before treatment. The plasma fibrinogen by the method of Wu⁵¹ was 0.37 per cent in the first month of treatment, and the sedimentation rate determined and transposed to a reference

TABLE 7.—*Studies of the Blood*

Date, 1928-1929	Serum Calcium, Mg. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Hemo- globin, per Cent	Red Blood Cells, Millions per C.Mm.
May 23.....	3.5
May 24.....	10.8*
May 25.....	11.2*
June 5.....	10.7	2.24	62	...
June 12.....	10.4	2.24	62	4.2
June 20.....	10.5	2.28	63	...
June 29.....	2.16	62	...
July.. 3.....	10.3	2.14
July 11.....	11.0	2.32	65	4.1
July 20.....	10.3	2.36
July 26.....	10.2	2.38	63	...
August 10.....	10.6	2.64	72	...
August 14.....	2.56
September 8.....	11.0	2.40	68	...
October 19... ..	10.1	2.30
November 21.....	10.1	2.40	75†	4.6
November 27.....	10.4	2.94	75†	4.6
January 2.....	10.9	2.21	85†	4.8
March 1.....	11.1	2.19	85†	4.3
March 22.....	10.9	2.59

* These determinations of calcium were made by the Clarke modification of the Kramer-Tisdall method (J. Biol. Chem. **63**: 461, 1925).

† These estimations of hemoglobin were made by the Talquist method; the others, by the Newcomer method.

hematocrit according to the method of Rourke and Ernstene⁵² was 0.61 mm. per minute. Both these figures are well above the upper limits found for healthy persons. Repetition of these determinations five months after treatment showed the normal value of 0.28 per cent for fibrin and a sedimentation rate of 0.1 mm. per minute. The abnormally high values of these measurements before treatment may have been associated with the pathologic changes in the bone, while the normal values

51. Wu, H.: A New Colorimetric Method for the Determination of Plasma Proteins, J. Biol. Chem. **51**:33, 1922.

52. Rourke, M. D., and Ernstene, A. C.: To be published.

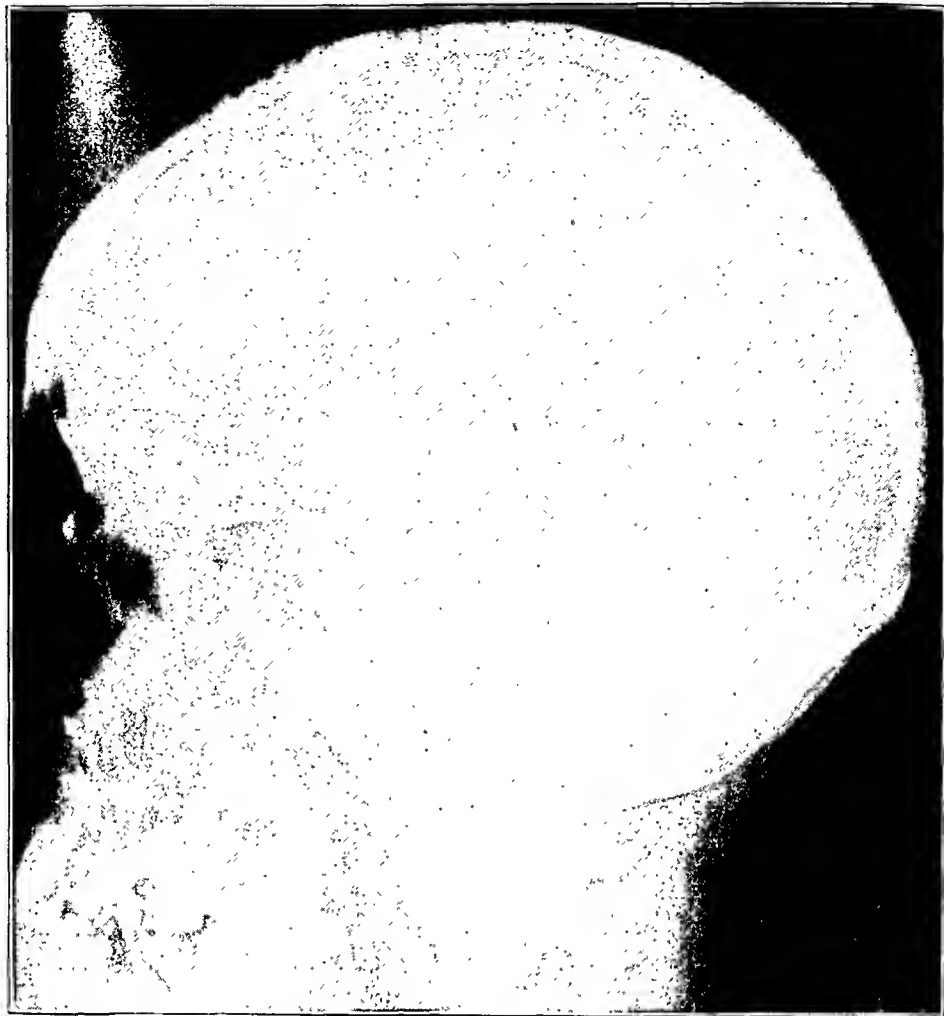


Fig. 2.—Roentgenogram of the skull before treatment.



Fig. 3.—Roentgenogram of the pelvis before treatment.



Fig. 4.—Roentgenogram of the hands, compared with a normal hand, before treatment.

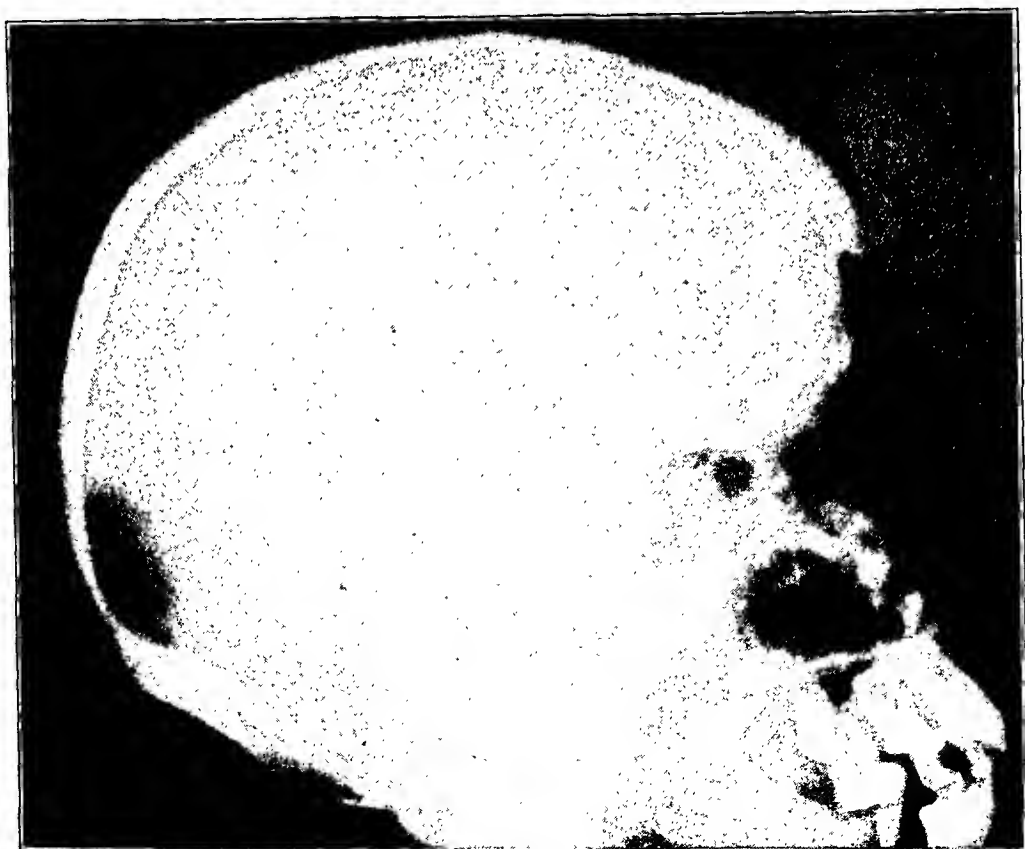


Fig. 5.—Roentgenogram of the skull after treatment.

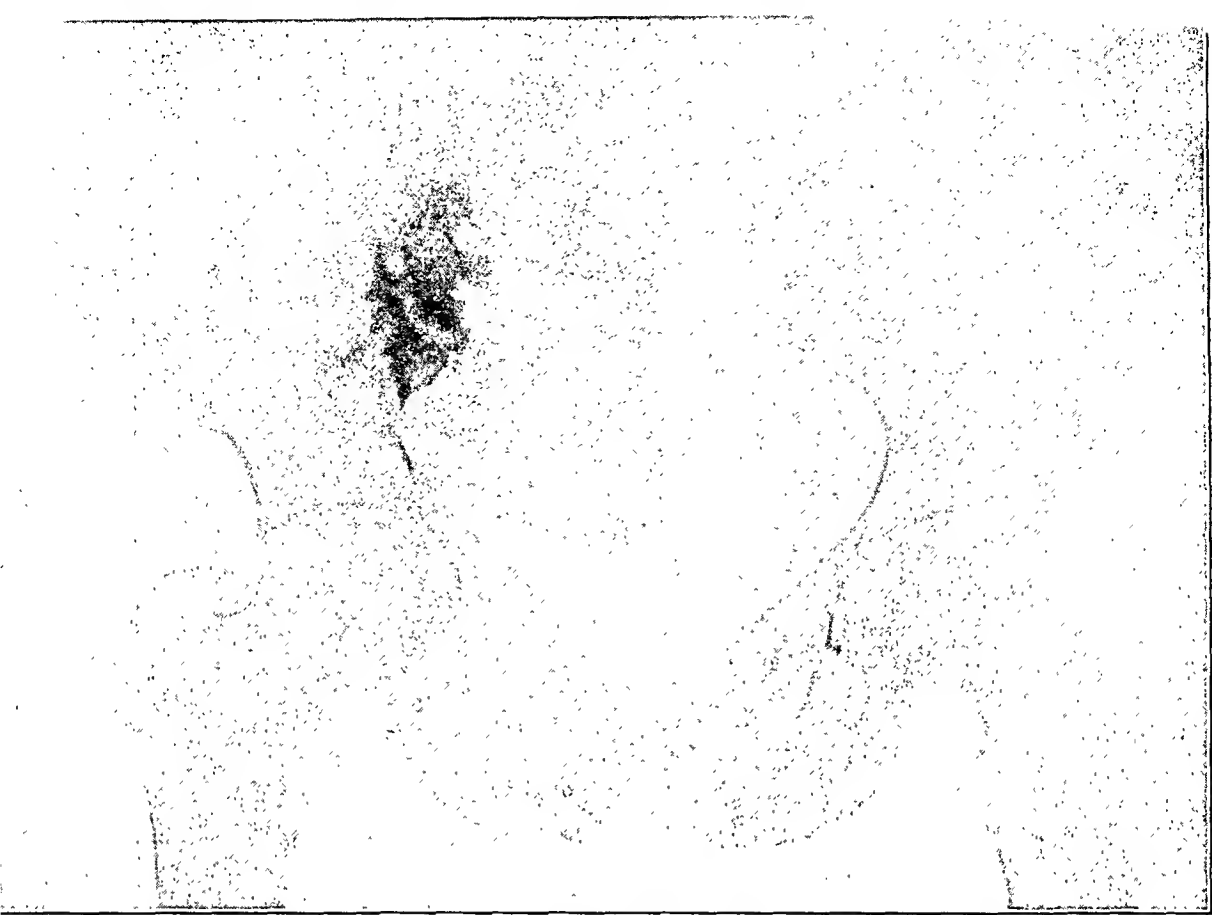


Fig. 6.—Roentgenogram of the pelvis after treatment.



Fig. 7.—Roentgenogram of the hands, compared with a normal hand, after treatment.

and after treatment are given in table 8. Of particular interest is her increase in height due partially to the application of proper braces and the correction of curvatures while the bones were still soft.

COMMENT

The patient aroused considerable clinical interest because of the extreme rarity of the condition in the United States. According to

TABLE 8.—Measurements of Patient

Parts of Body	June 1, 1928	Sept. 14, 1928	June 1, 1929
Head			
Diameters, Cm.			
Biparietal	11.0	14.0	13.5
Front of ears, 1 cm., and below parietal eminence, 4 cm.	11.5	14.5	14.5
Occipitofrontal	13.0	18.0	17.5
Root of nose to base of occiput	14.5	16.0	15.5
Between malars	9.0	12.0	12.0
Root of nose to tip of chin	8.5	12.0	11.5
Circumferences, Cm.			
Parietal	48.75	51.0	51.0
Just above ears	51.25	52.5	52.0
Through root of nose and occipital protuberance	50.6	51.0	52.0
Neck circumference, Cm.	28.75	29.0	30.0
Chest at nipple line, circumference, Cm.	71.25	88.0	87.0
Abdomen at umbilicus, circumference, Cm.	72.5	90.0	82.0
Pelvis			
Circumference, Cm.	77.5	89.0	86.0
Diameters, Cm.			
Interspinous	20.0	22.0	21.0
Interistal	26.0	29.0	27.0
External conjugate	17.0	21.0	20.0
External oblique	R 22.0 L 20.0	22.0 22.0	22.0 21.0
Extremities, length, Cm.			
Upper limb			
Upper arm	R 65.0 L 65.0	69.0 69.0	68.0 68.0
Forearm	R 26.25 L 26.25	28.0 28.0	30.0 30.0
Hand	R 23.1 L 23.1	24.0 24.0	24.0 24.0
Lower limb			
Thigh	R 15.6 L 15.6	17.0 17.0	14.0 14.0
Leg below knee	R 80.0 L 80.0	83.0 83.0	82.0 82.0
Foot	R 38.7 L 38.7	40.0 40.0	38.0 38.0
Body			
Total height, Cm.	R 35.0 L 35.0	37.5 37.5	36.0 36.0
Sitting height, Cm.	R 20.6 L 20.6	22.0 22.0	20.0 20.0
	148.0 70.6	151.0 71.0	158.0 76.0

Locke,⁵⁴ the disease is among the rarest of the bone diseases in this country. In 216,799 admissions to the Boston City Hospital during the years from 1915 to 1928, there were only 2 other instances of the disease. Although the incidence of osteomalacia is higher in women who have had repeated pregnancies than in other persons, it is excep-

54. Locke, E. A.: Osteomalacia, in Oxford Medicine, New York, Oxford University Press, 1927, vol. 4, p. 462.

tional for the disease to continue to progress steadily for several years following the termination of pregnancy.

The occurrence of such an extreme manifestation of the disease raised the expectation that endocrine or dietary factors might be revealed to account for the condition. No dietary deficiency or endocrine abnormality appeared obvious. On the contrary, in view of the remarkable effects following administration of 100 Gm. of cod liver oil reported by certain foreign observers, it was of particular interest that the patient's condition had become steadily worse in spite of 2 tablespoonfuls of unrefined, fresh cod liver oil every other day. The only evidence of endocrine imbalance was afforded by the history of the pseudocyesis, but the reliability of the patient proved too uncertain to allow emphasis on this phenomenon. Clinical and experimental evidence indicates that the pituitary gland and the ovaries are closely interrelated, and it may not be without significance that two instances of pseudocyesis which have recently come to the notice of one of us should have occurred in a patient with osteomalacia and in a patient with diabetes insipidus.

The disease as manifested in our patient corresponded with the advanced form observed in other parts of the world, in that the ribs, pelvis and long bones were particularly affected. The excruciating nerve root pain, the blue sclerotics, the anemia, the conspicuous muscular weakness, the "waddle gait" and the evidences of decalcification of the bone likewise were manifestations of the disease similar to those observed elsewhere. Unlike the patients studied by Miles and Feng³² in China, however, the level of the serum calcium was normal and that of the serum phosphorus was definitely lowered. The relation of the condition in our patient to "hunger osteomalacia" is uncertain, for the Viennese observers³⁵ noted an absence of deformities of bone and a disappearance of symptoms on administration of moderate doses of cod liver oil. While "hunger osteomalacia" may represent an early stage of the advanced form, nevertheless it seems that our patient should have been alleviated by the fresh, unrefined cod liver oil which she had taken for some months.

Whether the fundamental metabolic fault of the patient has been altered cannot be stated. While the patient excreted far less calcium and phosphorus in control periods 14, 15, 19, 20, 25 and 26 (table 6) than in periods 1 and 2 before treatment was instituted, this may have been due to a persistence of action of the immediately preceding therapeutic measures rather than to any fundamental change in metabolism. The fact that the abnormally low level of serum phosphorus has not changed during the year in spite of treatment and clinical improvement indicates that the fundamental metabolic fault has not been altered.

In the course of our study of this patient, we failed to discover any evidence of endocrine abnormality. Recently, Barr, Bulger and

the deposition of calcium. The fact that the retention of calcium became marked when ultraviolet light was given to our patient, in addition to cod liver oil concentrate, calcium and phosphorus, indicates again the similarity between our patient's osteomalacia and rickets. It is of interest in this connection that Steenbock⁵⁷ established the identity of irradiated ergosterol and vitamin D, and Goldstein³⁹ and Starlinger⁴⁰ reported clinical improvement in osteomalacia following the administration of irradiated ergosterol.

Blood Similarities.—The blood calcium of our patient was normal, while the blood phosphorus was definitely and persistently lowered, observations which again are in accord with observations in cases of rickets.⁵⁸

Because of these clinical, metabolic, x-ray picture and blood similarities, and because of the striking retention of calcium and phosphorus when ultraviolet light and vitamins A and D were given, we believe that osteomalacia, as manifested by this patient, is a form of rickets that occurs in adults.

SUMMARY AND CONCLUSIONS

1. A case of advanced osteomalacia occurring in a young American woman is reported.

2. The endogenous calcium, phosphorus and nitrogen metabolism were studied under rigidly controlled conditions, and the effect of various therapeutic agents was observed over a period of more than one year.

3. Whereas an average normal person receiving a diet low in calcium, low in phosphorus and low in vitamin has a negative calcium balance of 6.7 mg. per kilogram, the patient studied showed an average loss of 45 mg. of calcium per kilogram of body weight. The negative calcium balance persisted even when the patient received an amount of calcium greatly in excess of the normal metabolic requirements.

4. Previous to the time the studies were commenced, the patient's condition had become progressively worse in spite of her taking 30 cc. of fresh, unrefined cod liver oil on alternate days for six months before admission. The first therapeutic agent utilized during the study was 50 cc. daily of a physiologically tested preparation of cod liver oil.

57. Steenbock, H., and Nelson, M. T.: XIX. The Induction of Calcifying Properties in a Rickets-Producing Ration by Radiant Energy, *J. Biol. Chem.* **62**: 209, 1924.

58. Anderson, G. H.: The Calcium and Phosphorus Content of the Blood in Normal and Rachitic Children: I. Calcium, *Brit. J. Child. Dis.* **21**:33, 1924; II. Phosphorus, *ibid.* **21**:107, 1924.

This failed to cause an appreciable storage of calcium, although the amount given was much greater than that found effective in osteomalacia by other investigators.

5. When, however, a cod liver oil concentrate was fed so that the patient received very large amounts of vitamins A and D, improvement in the patient's condition became evident. This became even more conspicuous when ultraviolet light irradiation was added. Considerable amounts of calcium and phosphorus were deposited in the bones, as shown by the results of metabolism studies, as well as by the increased density of the bones according to the x-ray pictures. The tenderness of the bones and the anemia disappeared, and the patient showed striking clinical improvement under this treatment.

6. The storage of calcium and phosphorus was greatly increased by the addition of large amounts of these elements in the form of calcium lactate and disodium acid phosphate. When a preponderance of calcium was added to the diet, phosphorus, as well as calcium, was deposited in increased amounts. The converse occurred when a preponderance of phosphorus was added to the diet. Maximum retention occurred, however, when the increased amounts of both elements were fed simultaneously.

7. Observations on the phosphorus metabolism indicate that the calcium retained was deposited as bone.

8. The clinical, metabolic, blood and roentgen observations, together with the striking retention of calcium and phosphorus when ultraviolet light and vitamins A and D were given, lead us to believe that osteomalacia as manifested by this patient is a form of adult rickets.

LYMPHOSARCOMA

WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM *

CHARLES DAVISON, M.D.

NEW YORK

AND

JOSEPH J. MICHAELS, M.D.

DETROIT

* The brain and spinal cord are rarely the seat of direct invasion by lymphosarcomatous masses. Occasionally the structures about the central nervous system, such as the bones of the skull or the vertebrae, may show the presence of lymphosarcomatous nodules. Ewing¹ mentioned that with involvement of the cervical lymph nodes, the lesion may invade the wall of the pharynx, the tonsils and the base of the skull. Murchison,² in 1870, described a case in which a small growth existed in the dura mater above the foramen magnum, and Mosler,³ in 1872, found in another case some small lymphoid tumors above the optic foramen. Roncalli,⁴ in 1894, reported a case of lymphosarcoma with erosion of the base and dura. Guillain, Alajouanine and Perisson⁵ claimed to be the first to report lymphosarcomatous involvement of the spinal cord. The extramedullary masses found at operation compressed the cord, causing a complete paraplegia. Elsberg,⁶ in his book on tumors of the spinal cord did not mention any cases of compression of the cord due to these types of tumors. The scarcity of cases showing secondary involvement of the nervous structure, especially the report of only one case in the literature in which the spinal cord was compressed, is the reason for this presentation.

* Submitted for publication, Nov. 11, 1929.

* From the Neuropathological Laboratory, Montefiore Hospital, New York.

1. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922, p. 380.

2. Murchison, C.: *Case of Lymphadenoma of the Lymphatic System, Spleen, Lungs, Liver, Heart, Diaphragm, Dura Mater, etc.*, Tr. Path. Soc. Lond. **21**:372, 1870.

3. Mosler, F.: *Zur Histologie der Leukämie*, Virchows Arch. f. path. Anat. **56**:14, 1872.

4. Roncalli, F.: *Sarkom des Nasenrachenraumes*, Jahrb. u. d. Chir. Abt. d. Spit. zu Basel, 1892, p. 19.

5. Guillain, Alajouanine and Perisson: *Lymphosarcome extradural metastatique*, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1057, 1925.

6. Elsberg, C.: *Tumor of the Spinal Cord*, New York, Paul B. Hoeber, Inc., 1925.

trium and the back. In July, she had noticed a lump on the right hip followed by a sensation of tingling and numbness of the soles gradually ascending to the middle of the thighs and accompanied by weakness of the extremities. The past history was unimportant.

Examination.—Physical examination showed the patient poorly nourished and developed. There was lagging of the right side of the chest with dullness on percussion and tubular breathing posteriorly. The lymph glands of the neck and axillae were not palpable. Several hard masses, with rounded edges, were felt in the right iliac region and in the groins.

On July 31, 1924, the neurologic examination showed marked nutritional wasting of the musculature. The deep tendon reflexes were active and equal. There were a bilateral Babinski sign and all confirmatory reactions. The sensory examination showed diminished vibratory sense, a definite loss of the sense of muscle position and hypesthesia and hypalgesia from the tenth dorsal segment down. There was a belt of hyperalgesia between the eighth and tenth dorsal vertebrae. The abdominal reflexes were moderately active. Pain on pressure was elicited over the vertebrae between the seventh and eighth dorsal segments.

Laboratory Observations.—Roentgen examination of the chest revealed a pleural effusion at the right base extending to the sixth rib. The superior mediastinum on the left side showed an infiltrating mass suggestive of neoplasm. The blood count showed: hemoglobin, 70 per cent; red blood cells, 3,970,000; white blood cells, 11,200. The differential count was normal.

Course.—The patient received seventeen deep roentgen treatments of the various involved regions. With the exception of some improvement in the motion of the lower extremities and some recession of the glandular enlargement at the beginning of the administration of the rays, the symptoms became worse, and the patient died on October 23.

The anatomic diagnosis was generalized lymphosarcomatosis, right hydrothorax and fibrinous pericarditis.

Autopsy.—Gross Examination: The cervical lymph glands were slightly enlarged. A large mass in the anterior mediastinum was adherent to the sternum which in turn was replaced by tumor tissue. The bronchial root glands, those about the celiac axis and the chain along the vertebral column extending into the pelvis were all enlarged. The spinal cord showed a thickened dura with a flat friable tumor mass limited to the posterior surface of the lower dorsal and upper lumbar segments. When the cord was sectioned at this level, a translucency of the posterior and lateral columns was observed.

Microscopic Examination of the Tumor: The tumor consisted of fairly uniform, small, polygonal, irregular nuclei. In some instances, the latter were pale-staining and occasionally multilobulated, with a moderate number showing mitosis. Rarely was a syncytial cell found. In places the cells were small and round resembling lymphocytes. The masses of cells were separated by a delicate stroma.

At the ninth dorsal segment of the spinal cord, there was a demyelination of the posterior columns and the crossed pyramidal tracts. There was an ascending degeneration of the posterior columns above that level (fig. 1 *A*) and a descending degeneration of the crossed pyramidal tracts below the ninth dorsal segment (fig. 1 *B*).

The interesting features of this case were the rapid progression of the symptoms, the neurologic being the most outstanding; the absence of any enlargement of the glands of the neck until late in the disease, and

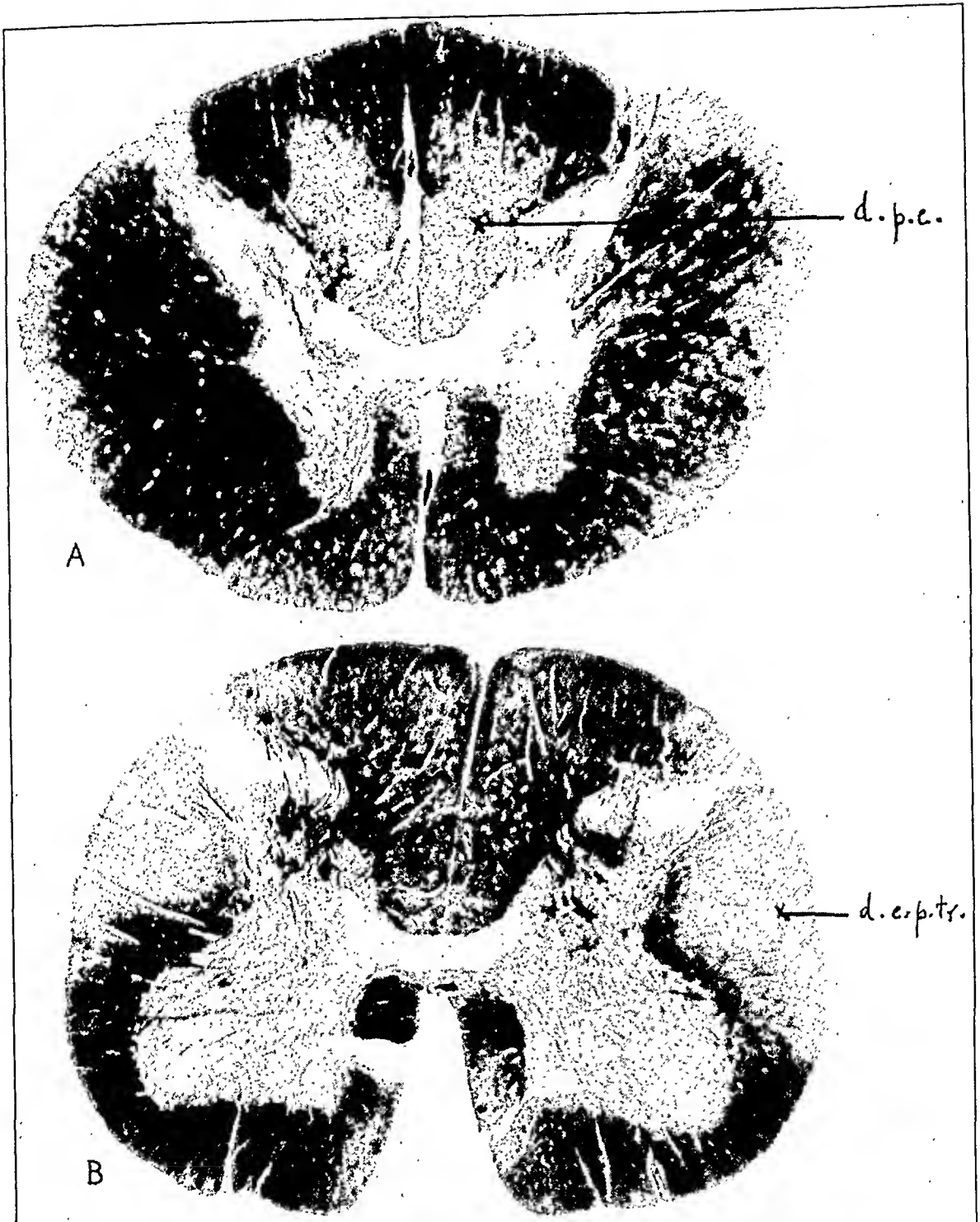


Fig. 1.—*A*, midthoracic region showing ascending demyelination of posterior columns (*d.p.c.*). *B*, lumbar region, showing descending demyelination of posterior pyramidal tracts (*d.c.p.tr.*). Weil stain; $\times 30$.

the occasional return in the power of the lower extremities owing to the recession of the tumor following deep roentgen therapy.

CASE 2.—D. S., a man, aged 40, a dress operator, was admitted to the Montefiore Hospital on Sept. 25, 1924. In April, 1924, he developed a dry cough, became dyspneic and felt somewhat weak. A diagnosis of pleural effusion was made. Pleural fluid was aspirated from his chest, following which he lost 16 pounds (7.3 Kg.) and developed a sharp pain in the lower right side of the chest. Fluid was repeatedly aspirated from the pleural cavity. A biopsy on a gland from the neck proved to be a lymphosarcoma. He received deep roentgen therapy which caused a disappearance of all the glands and improvement in his general condition, so that he was able to get about. In July, he became bedridden, his glands enlarged, he was markedly dyspneic, his feet were edematous and he developed a rash over the body and pains on both sides of the chest.

The past history was unimportant.

Examination.—Physical examination showed a bedridden and dyspneic patient with the knees flexed on the abdomen. The glands of the neck were enlarged bilaterally. The tonsils were extremely enlarged, red and cryptic and almost met in the midline. Enlarged, discrete, rubbery glands were found on either side of the face. The chest was asymmetrical, the left side being fuller than the right and expanded poorly. There were diminished fremitus on the left side, dullness on percussion from the third rib down anteriorly and posteriorly and diminished breathing on both sides, more marked on the left. A systolic murmur throughout the precordium, with the greatest intensity in the apex, was transmitted to the axilla. The liver was palpable on the right side four fingerbreadths below the costal margin. The lower extremities showed edema of both ankles, feet and legs.

Neurologic examination was rather unsatisfactory. All the deep reflexes were absent. Over the region of the fourth and fifth ribs there was a herpetic eruption.

Laboratory Observations.—Roentgen examination showed old calcareous deposits in the right apex and hilar region. There was evidence of fluid in the left side of the chest. Inoculation of the pleural exudate into a guinea-pig gave negative results. All other laboratory examinations were negative.

Anatomic Diagnosis.—The diagnosis was generalized lymphosarcomatosis, hydrothorax, bilateral hydro-ureter and hydronephrosis.

Autopsy.—Gross Examination: In the region of both parotid glands, firm masses were felt which were continuous with bulgings in the submaxillary, posterior cervical region and supraclavicular nodes, forming a complete collar around the neck. Over the lower lobe of the right lung both pleurae were thickened and separated by an edematous, infiltrating, fibrous tumor which invaded the parenchyma of the lung only at the hilus, surrounding the larger vessels and bronchi and extending several centimeters into the depth of all three lobes. From the region of the hilus the tumor extended from the base of the skull to the coccyx, along the lateral surfaces of the bodies of the vertebrae, and filled the pelvis covering its lateral walls, surrounding in its course the aorta, ureters, nerve fibers, pelvic vessels and organs. In addition, the tumor had extensively infiltrated the omentum, appendix and cecum. The glands in the root of the mesentery and around the celiac axis, axillary and inguinal nodes were also replaced by tumor.

Microscopic Examination: The microscopic structure of the tumor was somewhat similar to that described in case 1. During the removal of the spinal cord,

neoplasm. The deep roentgen treatment caused disappearance of the glandular enlargement and gave the patient some relief from his symptoms.

CASE 3.—J. K., a man, aged 32, a salesman, was admitted to the Montefiore Hospital on April 11, 1921. In October, 1920, the patient began to cough and expectorate greenish sputum, which symptoms subsided in January, 1921. Following this he noticed a gradual numbness of the neck, arms, back, chest, abdomen and legs. He had formication limited to the upper extremities, left lumbar region of the abdomen and the feet when in motion. There was a gradual loss of weight and wasting of muscles. During the last month before admission to the hospital he had considerable difficulty in walking, ataxia, constipation and frequency in micturition.

Examination.—The patient was markedly emaciated and pale and had a slight exophthalmos. On percussion, the chest showed dullness of the apex posteriorly and flatness down to the sixth rib. The breath sounds on the right were diminished anteriorly to the third rib and were absent posteriorly. All the other organs were normal.

On neurologic examination, the pupils were found to be dilated and slightly irregular, reacting to all stimuli. There was nystagmus in all directions. There was nutritional atrophy of all the muscles of the body. The upper and lower extremities were markedly ataxic. There were athetoid movements of the fingers. All the deep reflexes, such as the biceps, triceps, knee and ankle reflexes could not be elicited. The lower abdominal reflexes were absent. The cremasteric reflex could not be elicited on the right. The Babinski sign, allied reflexes and ankle clonus were absent. There was loss of position and vibratory sense up to the fourth dorsal segment. There were hypalgesia and hypesthesia from the sixth dorsal vertebra down with vague sensory disturbances above the sixth segment and a suggestion of a belt of hyperalgesia between the fourth and the sixth segments.

Laboratory Observations.—Roentgen examination of the chest showed the lower one third of the right lung completely obscured by a dense homogeneous shadow suggesting a neoplasm. The blood count showed: hemoglobin, 80 per cent; red blood cells, 3,520,000; white blood cells, 12,800. The differential count was normal. All other laboratory data were negative.

Course.—The patient received numerous administrations of deep roentgen therapy. During the early course of the treatments, there was a disappearance of the enlarged glands and some of the symptoms, especially the pain. Later the glands enlarged and failed to respond to treatment, and the patient died on May 28.

Diagnosis.—The diagnosis was: neoplasm of the right lung with secondary deposits in the cord. There was a possibility of subacute combined degeneration. The anatomic diagnosis was: lymphosarcoma of the root of the right lung, bronchopneumonia and empyema.

Autopsy.—Gross Examination: The lower lobe of the right lung, near the hilus, showed a cauliflower-like mass projecting beyond the pleural surface. At the root of the lung there was a hard, white tumor mass roughly 7 cm. in diameter which had eroded and completely obstructed the hyparterial bronchus. The two lower lobes were riddled with cavities varying in size from 0.5 to 2 cm., filled with a foul-smelling, dark yellowish-green, purulent material. The peribronchial lymph glands were soft and enlarged.

The microscopic appearance of the tumor tissue was that of a lymphosarcoma.

paresis occurred, which improved ten days following deep radium therapy. The glandular nodules also showed temporary recession. During the course of the roentgen therapy, a crop of subcutaneous nodules appeared; the patient was then admitted to the hospital. Subsequently he developed a weakness of the entire left side of the body and a hypesthesia over the left side of the face and tongue.

Examination.—Physical examination revealed a markedly emaciated man, presenting numerous discrete tumor nodules involving the cranium and the cervical, axillary and inguinal glands. The glands were discrete and freely movable, varying in size from that of a pea to that of a large hazelnut. Those that were primarily intracutaneous were firm in consistency. The heart and lungs were

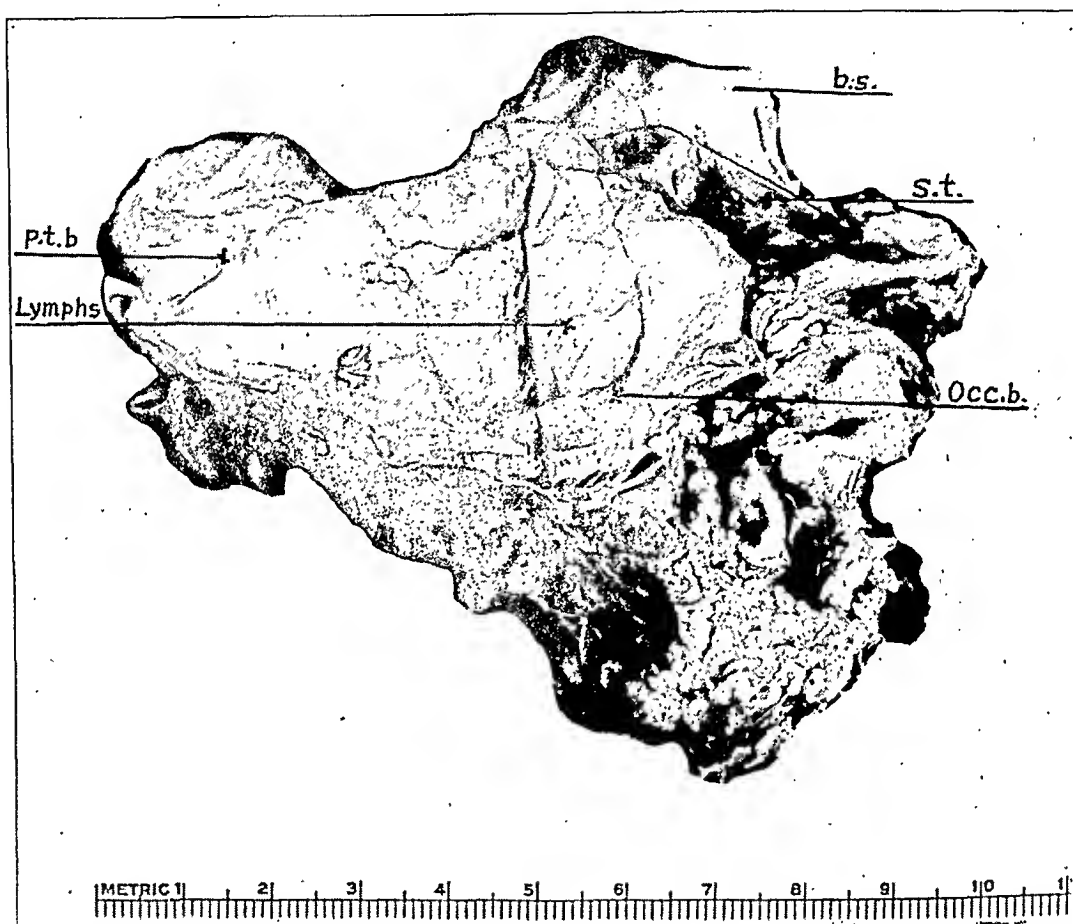


Fig. 4.—Lymph node occupying part of the basilar portion of the occipital bone and the left posterior surface of the petrous portion of the temporal bone. *b.s.* indicates the body of the sphenoid; *s.t.*, the sella turcica; *occ.b.*, the basilar portion of the occipital bone; *p.t.b.*, the posterior surface of the petrous portion of the temporal bone; *lymphs.*, lymphosarcoma.

normal. The liver was enlarged four fingerbreadths below the right costal margin and presented a large, irregular, nodular mass below the free edge. Perianal nodules were present. There was localized tenderness over the upper part of the left femur and over the left scapula posteriorly.

Neurologic examination revealed blurring of the margin of the left disk on the nasal side, weakness of the left external rectus and a suggestion of anisocoria.

There was hypalgesia of the first and second portions of the left fifth nerve without involvement of the motor portion. All the tendon reflexes on the left were definitely diminished. There were no abnormal reflexes. There was generalized muscular wasting with a weakness of the left side of the body, more marked in the upper than in the lower extremities.

Laboratory Observations.—Roentgen examination of the skull disclosed a small area of bone absorption in the parietal region, possibly metastatic. There were pulmonary metastases, and the mediastinal glands were enlarged. A biopsy taken on Feb. 16, 1929, showed the mass to be a lymphosarcoma.

Course.—During the patient's stay in the hospital, he received four deep roentgen treatments, chiefly for the alleviation of the excruciating lumbosacral pain. The only effect was temporary recession of the glandular nodules. Irra-

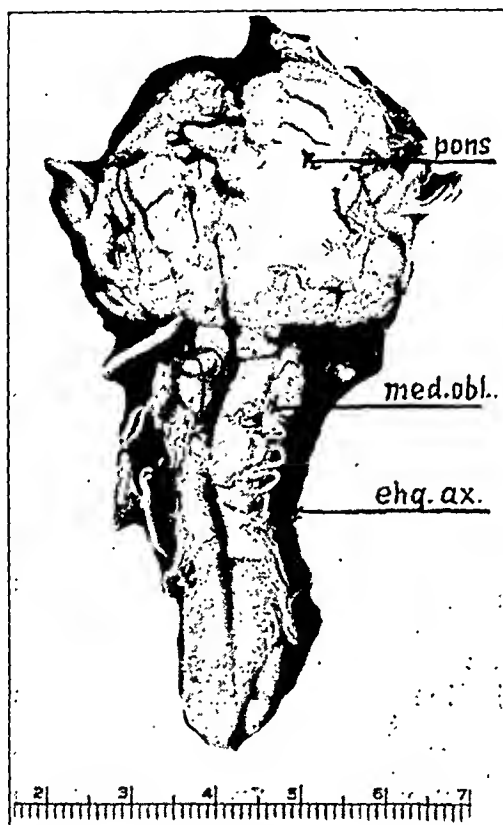


Fig. 5.—Distortion of the pons (*pons*) and medulla oblongata (*med. obl.*) due to compression by the lymph nodes as shown in figure 4. Change in the axis (*chg. ax.*) of the medulla oblongata due to compression.

diation of the cervical and upper dorsal spine had no effect. Typhoid vaccine was also administered without any results. A biopsy taken in February showed the tumor to be a lymphosarcoma. The patient died on March 10.

Diagnosis.—The diagnosis was general lymphosarcomatosis with involvement of the meninges at the base of the skull, extending from the middle fossa downward. The anatomic diagnosis was lymphosarcoma with metastases to all the organs and invasion of the sella turcica.

Autopsy.—Gross Examination: All the lymph nodes were enlarged and readily palpable. Irregular swellings were palpable on the top of the cranium. The paravertebral and prevertebral lymph nodes were everywhere markedly enlarged

and firmly fused with their adjacent glands. In the calvarium several irregular thickenings were fused to the periosteum. In the left wall of the sella turcica a lymph node occupied part of the basilar portion of the occipital bone and the left posterior surface of the petrous portion of the temporal bone (fig. 4). This mass compressed and distorted the pons and medulla oblongata (fig. 5). Another lymph node continuous with the former occupied the portion of the left anterior surface of the petrous portion of the temporal bone and the left sphenoid bone at the clinoid process (fig. 6). When the tumor mass was sawed through, the bony structure was found to be invaded by the lymphosarcoma. Near the foramen magnum there was another small lymphoid mass attached to the dura.

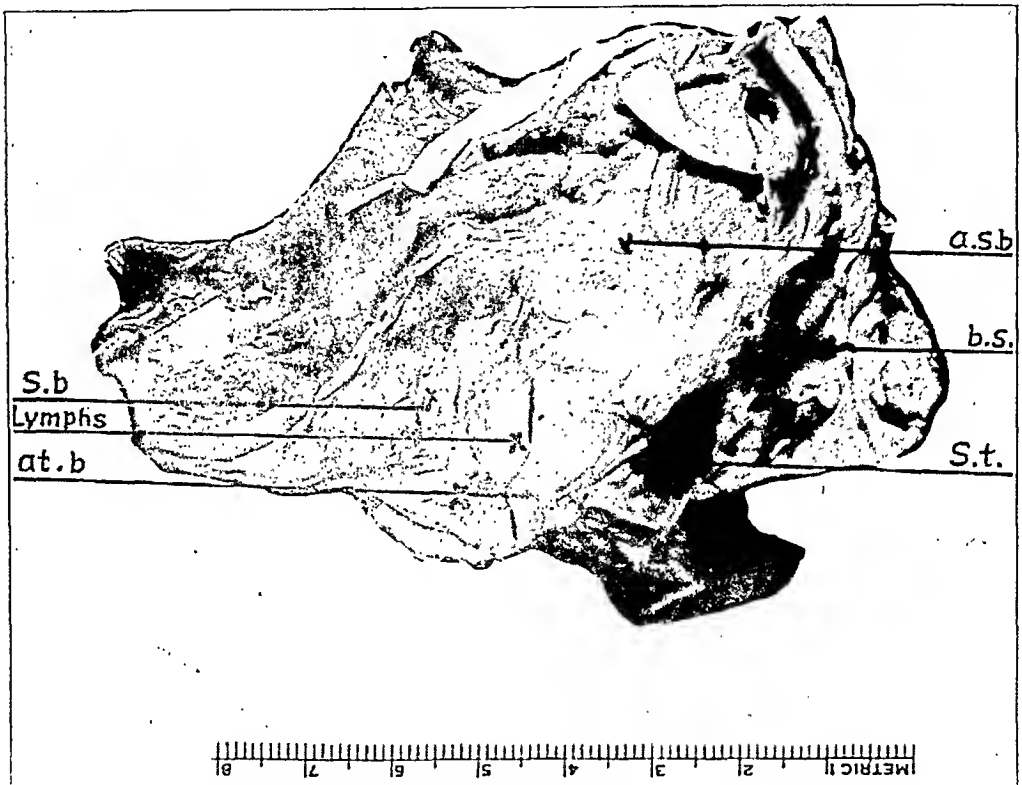


Fig. 6.—Lymph node occupying the left anterior surface of the petrous portion of the temporal bone and left sphenoid bone. *a.s.b.* indicates the ala of the sphenoid bone; *b.s.*, the body of the sphenoid; *s.t.*, the sella turcica; *s.b.*, the sphenoid bone; *a.t.b.*, the anterior surface of the petrous portion of the temporal bone; *lymphs.*, the lymphosarcomatous nodule.

The brain, with the exception of a depression of the left side of the temporal lobe caused by the tumor mass, appeared to be normal on the surface. When the brain and the spinal cord were sectioned, no abnormalities were observed.

Microscopic Examination: Examination of the tumor mass of the skull showed it to be a lymphosarcoma. Sections of various regions of the brain stained by special preparations revealed no abnormalities.

The left side of the pons showed a marked flattening, especially at the exit of the trigeminal nerve (fig. 7). With the Weil method, no areas of demyelination were observed, with the exception of part of the fibers of the fifth nerve

on the left side. With the hematoxylin and eosin and cresyl violet methods, the nerve cells of the nuclei of the fifth nerve showed a slight amount of pigment atrophy. The nerve cells of the sensory portion of the left fifth nucleus were somewhat atrophic and shrunk, and the Nissl substance stained poorly with the selected stains (figs. 8 and 9). A few nerve cells of the nucleus of the left sixth nerve showed similar changes.

Sections from the cervical region of the cord showed some of the cells of the anterior horns, especially the dorsolateral group, to be slightly swollen, with a disappearance of the Nissl substance.

Microscopic Diagnosis.—The diagnosis was lymphosarcomatous invasion into the skull causing compression of the pons and medulla oblongata.

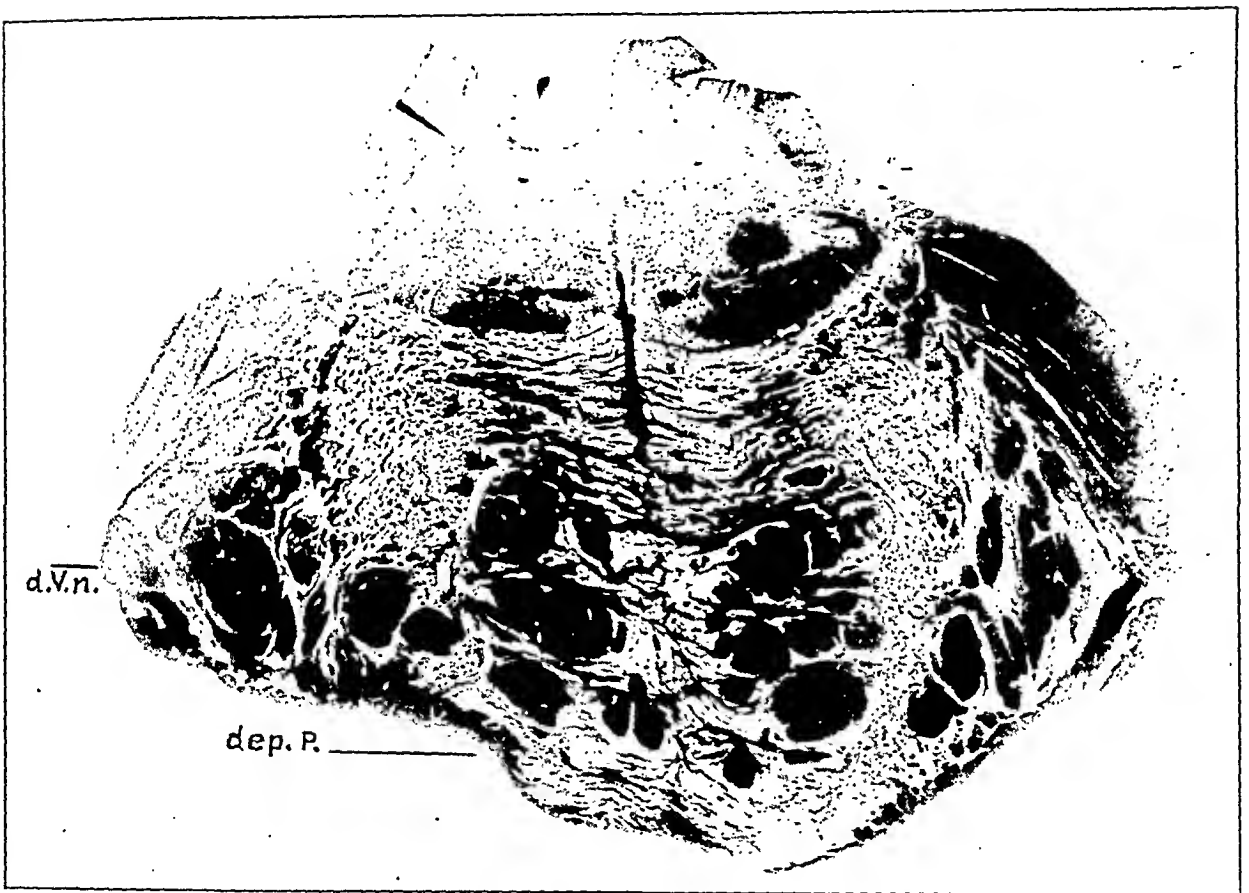


Fig. 7.—Flattening of the left side of the pons. Demyelination of the fifth nerve (*d.V.n.*); depression of the pons (*dep.p.*) from the compression of the lymphosarcomatous nodule.

The tumor masses found in the other organs revealed the same microscopic characteristics as the metastasis to the skull.

The important features of this case were: the recession of some of the lymph glands without deep roentgen treatments and the involvement of the skull, especially of the middle and posterior fossa. The anisocoria was probably due to the compression of the left cervical sympathetic by the tumor. The sensory changes of the left fifth and the left external rectus palsy were due to secondary changes in the nuclei of those nerves due to compressions, as illustrated in figures 7, 8 and 9. The duration of the disease in this case was about two years.

Group 2: Cases of Lymphosarcoma Presenting Neurologic Signs Which Did Not Come to Autopsy.—CASE 5.—E. L., a man, aged 64, was admitted to the Montefiore Hospital on April 18, 1922. Following a toothache in September, 1921, a large swelling occurred on the opposite side of the face and neck. A biopsy from this swelling was diagnosed as tuberculosis. In January, 1922, a piece of tissue from the same area was diagnosed as lymphosarcoma. Since then the patient had difficulty in breathing and choking sensations. He received several treatments with radium followed by diminution in the size of the tumor

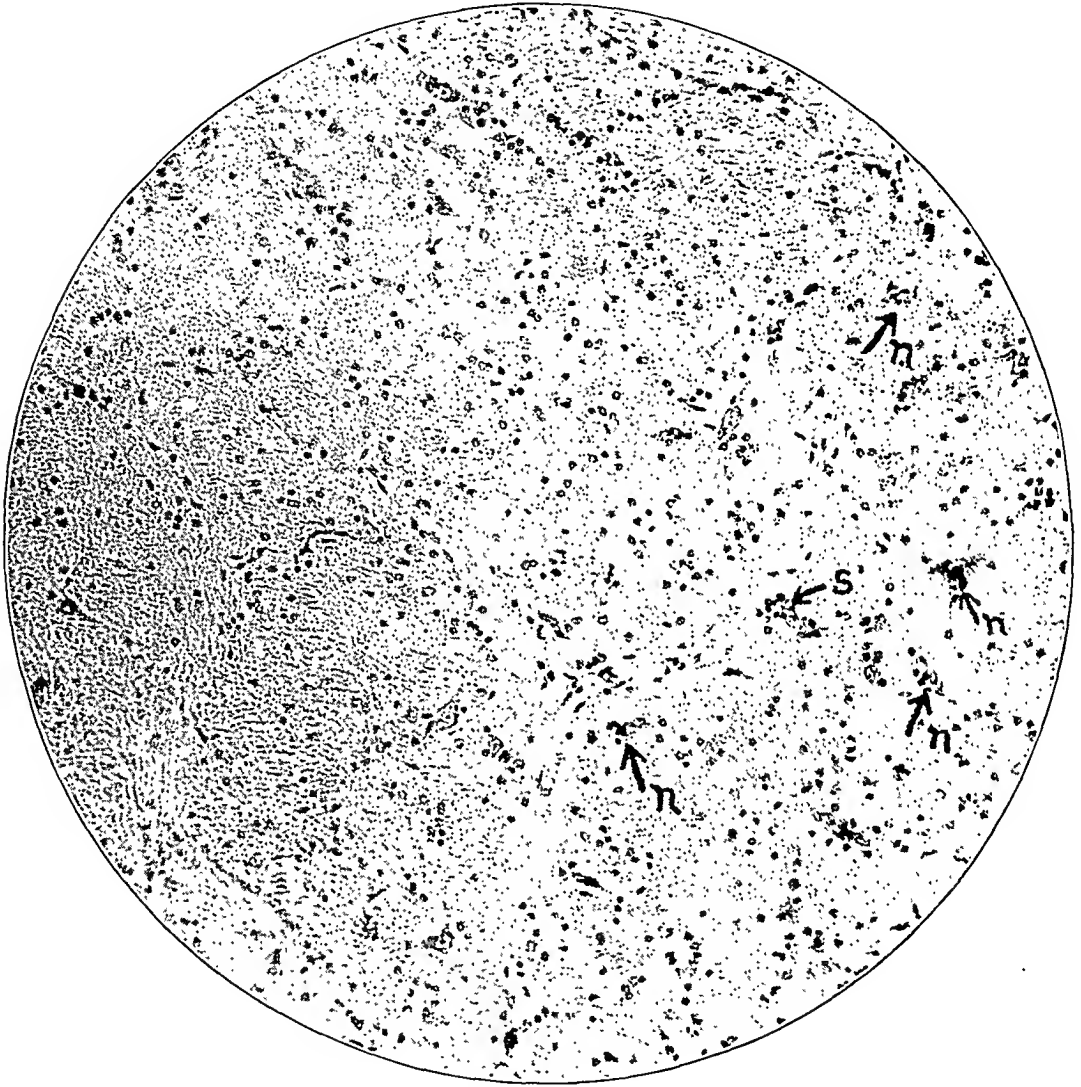


Fig. 8.—Section from the sensory portion of the nucleus of the fifth nerve showing degeneration of nerve cells. *n* indicates neuronophagia; *s*, satellitosis. Cresyl violet stain; $\times 300$.

and disappearance of the difficulty in swallowing. In June, he had diplopia and disturbance in vision of the right eye, followed by insomnia and generalized weakness.

Examination.—Physical examination revealed an emaciated, anemic looking man. A large, hard mass bulged from the right side of the pharynx into the right pharyngeal cavity. The uvula was displaced to the left, its upper pole

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reaching the level of the palate. The movements of the neck were limited and painful. There was a large swelling on the right side of the neck. Both supra-clavicular fossae showed enlarged glands, firm in consistency. The movements of the right side of the chest were limited with an area of dulness in the left axillary region below the sixth rib. The breath sounds were normal. The liver was enlarged.

Neurologic examination showed a slight tic of both eyelids, more marked on the right. The pupils were irregular and reacted somewhat sluggishly to light,

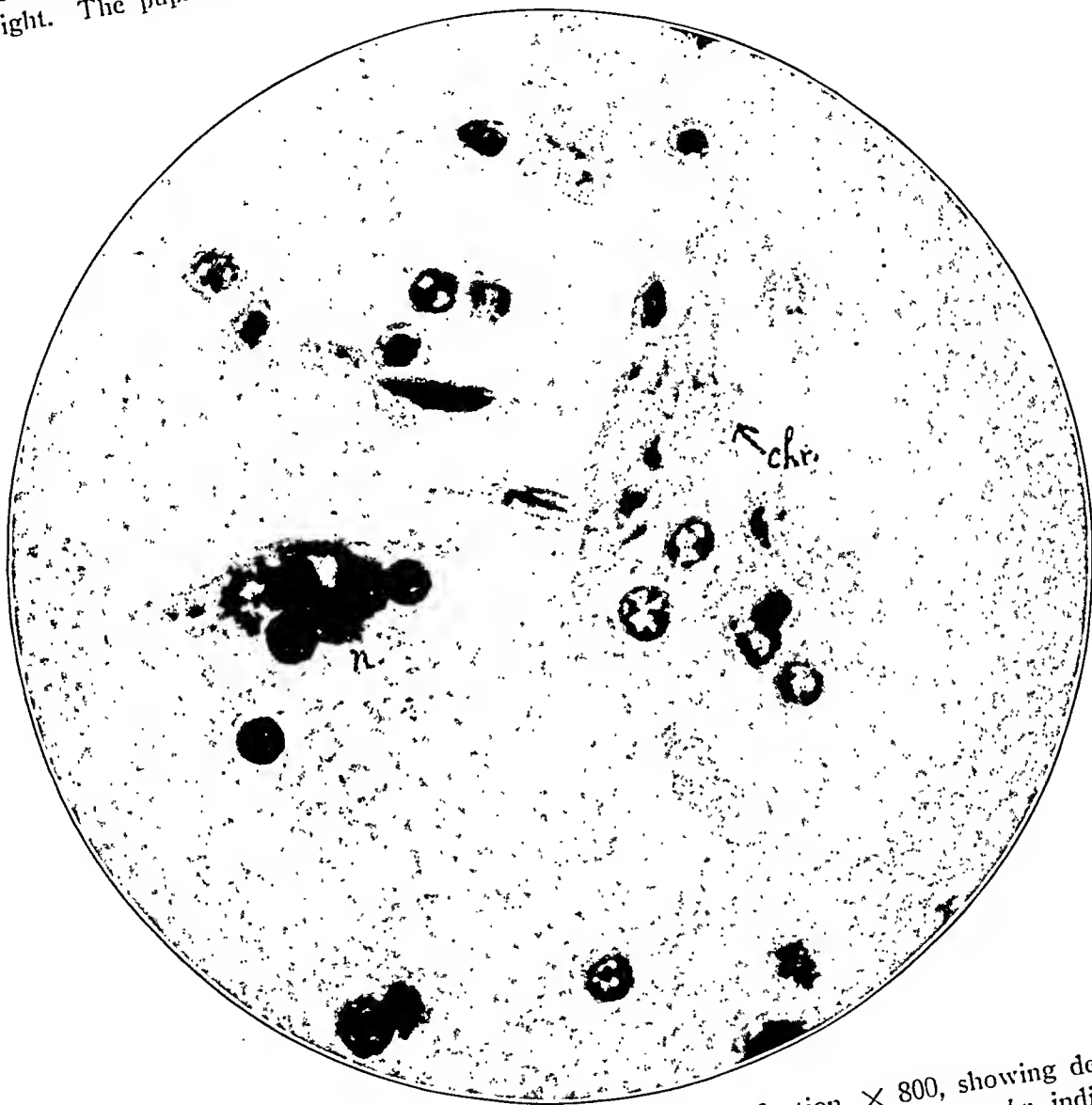


Fig. 9.— Same as figure 8 under higher magnification, $\times 800$, showing degeneration of the nerve cells and disappearance of the Nissl substance. *chr.* indicates chromatolysis; *n.*, beginning neuronophagia.

but well in accommodation. There was paralysis of the right external rectus. There was corneal hypesthesia on the right side. The tongue deviated to the right. The left margin of the tongue was definitely thinner than the right, with fine fibrillary twitchings. There was apparently no paralysis of the palate or uvula. Hearing on the right side was diminished, bone conduction being better

in the right ear. The entire musculature of the body showed general wasting and poor tonus. All the deep reflexes were present and equal on the two sides.

Laboratory Observations.—The blood count showed: red blood cells, 3,300,000; white blood cells, 6,000; hemoglobin, 80 per cent; the differential count was: polymorphonuclear leukocytes, 70 per cent; small lymphocytes, 2 per cent; large lymphocytes, 22 per cent; eosinophils, 6 per cent.

The roentgenogram showed small areas of infiltration in both apexes and an old thickened pleura in the left base.

Course.—The patient was in the hospital at various intervals, where he received twenty-nine applications of radium. The general condition of the patient was improved, and the tumor decreased in size, enabling him to eat and to return to his work. The enlargement recurred at times. He has not been heard from since November 27.

Diagnosis.—The diagnosis was lymphosarcoma with invasion of the dura in the posterior fossa causing compression of the cranial nerves.

This case presented early involvement of the cervical lymph nodes, with definite involvement of the nervous structures in the posterior fossa. The general physical signs as well as the neurologic symptoms disappeared following intensive radium therapy. The patient has not been heard from since 1922. This case falls in the same group as case 4, group 1.

CASE 6.—L. C. R., a man, aged 37, a contractor, was admitted to the Montefiore Hospital on July 11, 1922. In April, 1922, the patient had experienced a dull, dragging sensation in the left side of the abdomen radiating to the back and the left hypogastric region. The abdominal pains became worse, and in May an exploratory laparotomy was performed at which time a retrocecal, kinked appendix was removed without relieving the patient from his symptoms.

In April, 1921, he had dysentery, with a temperature of 102 F.

Examination.—Physical examination showed a chronically ill patient in great pain, with an enlargement of the cervical and submaxillary glands. The heart, lungs and all other organs were normal.

Neurologic examination showed an area of hyperalgesia between the ninth and tenth dorsal segments on the left side, confined to the anterior divisions of the posterior roots, i. e., beginning anteriorly about the midline and terminating at the postaxillary line. There was tenderness over the eighth, ninth and tenth dorsal vertebrae. With the exception of lively achilles' reflexes and a suggestive ankle clonus on the left, all the other observations were negative.

Laboratory Observations.—Roentgen examination of the chest showed a dense uniform shadow over the entire left side. The structure of the lung in back of this shadow could not be distinctly seen, but there was apparently some infiltration in the region of the lower lobe.

On July 20, 45 cc. of clear spinal fluid was removed under increased pressure. There were 30 cells, mostly lymphocytes. The fluid showed a slightly positive globulin reaction and a faint reduction with Fehling's solution. A microscopic examination of pleural exudate revealed tumor cells.

Course.—Following a diagnosis of an extramedullary tumor of the spinal cord, the patient was sent to the Neurological Institute, where a laminectomy was performed by removal of the eighth, ninth and tenth dorsal vertebrae, without finding any pathologic process at this level. The ninth, tenth and eleventh left

the left brachial plexus. The roentgenogram showed evidences of metastases to the lower dorsal spine.

COMMENT

An analysis of twenty-six cases of lymphosarcoma from the Montefiore Hospital since 1922 showed seven cases with involvement of the central nervous system. Of nine cases that came to autopsy, four showed lesions of the central nervous system. Fifteen of the twenty-six patients were males and eleven females. Their ages ranged from 36 to 60, the average being 45 years. The oldest patient was 74, the youngest 11 years. The average life from the onset of the disease in the cases presented was one year and ten months. The longest duration of the disease in one case was seven years, and the shortest five months. Twenty-three of the patients died, two are still living and one could not be followed up. Desjardins and Ford,⁸ in an analysis of fifty-five patients with lymphosarcomas who died, found the average duration of the disease from the onset of symptoms to be two years and five and one-half months.

Two of the seven cases showing neurologic signs showed invasion (cases 4 and 5) of the cranial cavity localized chiefly in the middle and posterior fossae; four showed involvement of the vertebral column or the spinal meninges which caused compression of the spinal cord or the posterior roots, resulting in herpes zoster (as in case 2), and one case showed involvement of the facial nerve peripherally (case 7). Woltman,⁹ in a series of tumors of the nasopharynx, reported six cases of lymphosarcoma with involvement of the cranial nerves, but none of these cases came to autopsy. Our series of cases showing secondary compression of the spinal cord or the posterior roots is the largest, the only other case reported being that of Guillain.⁵

Cases 4, 5 and 7 showed early involvement of the cervical lymph nodes, in two (cases 4 and 5) of which the cranial cavity was invaded. In the other cases, the invasion of the glands of the neck did not occur until late in the disease.

In case 4, in which the cranial cavity was invaded, the brain tissue itself did not show any evidences of invasion by the lymphosarcoma, as is usually seen in metastasis from other tumors, especially metastatic carcinomas. The invasion in this case took place by way of the lymphatics. As the brain proper is not supplied by lymphatics, this readily explains the absence of invasion of the brain tissue by lymphosarcomas or Hodgkin's disease. The cases showing involvement of the spinal

8. Desjardins, A. U., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, *J. A. M. A.* **81**:925 (Sept. 15) 1923.

9. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, *Arch. Neurol. & Psychiat.* **8**:412 (Oct.) 1922.

cord in the form of compression did not show enlarged cervical lymph glands until late in the disease. In none of these cases was the spinal cord directly involved.

All of the seven patients treated by deep roentgen and radium therapy, with the exception of the patient in case 7, showed a recession of the lymphosarcomatous masses with improvement in the symptoms only early in the treatment. After a few treatments, the enlargements and symptoms recurred and finally failed to respond. This is characteristic of all lymphosarcomas.

CONCLUSION

Twenty-six patients with lymphosarcoma admitted to this institution since 1922 were investigated, seven of whom presented neurologic signs and symptoms. Four of these patients showed signs of compression of the spinal cord. The literature on this subject reports only one case.

In none of the cases was there a direct invasion of the brain or the spinal cord. The symptoms were due chiefly to compression from invasion of the skull, vertebrae or meninges.

Invasion of the cranial cavity took place only when the cervical lymph nodes were involved, and, as observed in our series, involved early.

Deep roentgen and radium therapy, while not a cure for the disease, causes some relief from the symptoms during the first few applications. The relief is due chiefly to the recession of the tumor, which causes compression on the respective organs. When these enlargements fail to respond to treatment, improvement in the symptoms may not be expected. For a time, however, these patients benefit a great deal by deep roentgen or radium therapy, and at present these are the best forms of palliative treatment.

SPONTANEOUS RECOVERY FROM PERFORATION OF PEPTIC ULCER INTO THE FREE ABDOMINAL CAVITY*

HARRY A. SINGER, M.D.

CHICAGO

Spontaneous recovery following perforation of a peptic ulcer into the free abdominal cavity is and has been generally considered of rare occurrence. Older writers attempted to account for the occasional recovery without operation by the absence of food in the stomach at the time rupture occurred. Thus, Hall,¹ who reported one and collected six additional cases of spontaneous recovery, ascribed the outcome to the empty state of the stomach when the perforation took place. He concluded, "When perforation of a presumably full stomach has occurred laparotomy affords probably the only chance." Pariser² was also greatly impressed by the importance of the presence or absence of food in the stomach in determining the fate of a perforated ulcer. In fact, he recommended considering as the time of onset in the case of a fasting stomach not the moment of actual perforation but the time food or liquid was ingested subsequent to rupture. The clinical investigation of Brunner³ cast doubt on the belief that death was imminent unless the stomach was empty at the time of perforation. Brunner was able to collect several cases in which recovery supervened, although the stomach was not entirely devoid of food when perforation occurred. He agreed, however, that spontaneous recovery after perforation into the free abdominal cavity was quite exceptional, stating that it occurred at the most in 5, and in all likelihood, a much smaller percentage of cases in which operation was not performed. Speck,⁴ in a more recent comprehensive review of the subject of perforation of peptic ulcer into the free abdominal cavity, stated that according to the new statistics only one or two of every hundred patients recover spon-

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* From the Department of Medicine, University of Illinois College of Medicine and the Cook County Hospital.

1. Hall, W. W.: A Case of Perforating Gastric Ulcer: Peritonitis; Recovery, *Brit. M. J.* **1**:64, 1892.

2. Pariser, C.: Zur Behandlung des frei in die Bauchhöhle perforierten Duodenalgeschwürs, *Deutsche med. Wchnschr.* **21**:450 and 466, 1895.

3. Brunner, F.: Das acut in die freie Bauchhöhle perforierende Magen- und Duodenalgeschwür, *Deutsche Ztschr. f. Chir.* **69**:101, 1903.

4. Speck, W.: Zur Klinik und Pathologie der in die freie Bauchhöhle perforierten Magen- und Duodenalgeschwüre, *Beitr. z. klin. Chir.* **129**:537, 1923.

taneously. Practically all modern textbooks and systems, not only of surgery but also of medicine, voice essentially the opinion expressed by Speck.

A few years ago, following routine study of a series of patients with acute abdominal pain, I arrived at the conclusion that death from ulcer was by no means the invariable outcome when operation was not performed. As my experience increased, I became more and more impressed by the belief that recovery without operation following perforated peptic ulcer was not of infrequent occurrence. At first with timidity, but later with assurance, I made the clinical diagnosis of perforated ulcer with spontaneous recuperation in cases in the wards. Since my associates repeatedly questioned the correctness of this diagnosis, I decided to record and collect the records of the cases which I considered instances of spontaneous recovery following perforation into the general abdominal cavity. Through the courtesy of my colleagues on the staff at the Cook County Hospital, I was privileged to use the material in the several medical and surgical wards. Within a period of approximately eighteen months, beginning with the spring of 1928, I observed forty cases in which the diagnosis of spontaneous recovery seemed warranted. In all probability, there were treated in the hospital during the same period other patients with more or less identical cases, who, however, did not come under my observation.

The cases gathered in the course of this study can be conveniently arranged in four groups. The first group includes those cases of ruptured ulcers in which the presence of a perforation recently obturated, sealed or covered, was demonstrated at operation undertaken within a short time after the accident occurred. The second group comprises cases of chronic ulcer in which an antecedent history of acute perforative peritonitis was obtained, and in which at operation, performed after a lapse of time, old adhesions, presumably due to a previously perforated ulcer, were found. In the third group are cases with the history of a chronic ulcer, signs and symptoms of perforation and the presence of free intraperitoneal air demonstrated by means of roentgenograms shortly after the onset of acute symptoms. In the fourth group, both operative and roentgen evidence of a ruptured viscus is lacking, the diagnosis being based on the history of a chronic ulcer, the clinical symptoms and signs of a perforative peritonitis and the roentgenologic demonstration after subsidence of the acute symptoms of a gastric or duodenal lesion. The evidence for considering the cases in all four groups as instances of free perforation with spontaneous healing is submitted here together with case reports. To avoid unnecessary repetition, since some of the cases are practically identical, not all of the forty cases are described. Twenty cases, five from each group, selected to represent the most diversified in the series, seem sufficient for illustrative purposes.

Only the data that deal directly with the phase of ulcer under consideration are included in the following case reports. It should be constantly borne in mind that the history as subsequently recorded represents in many instances the wheat sifted from a great deal of chaff. In a considerable proportion of the cases, the information volunteered by the patient and the history as written by the intern bore little resemblance to the anamnesis. Direct questioning, after the physical observations led to the suspicion of a perforated ulcer, in not a few cases was the means of obtaining the characteristic history presented to the reader.

GROUP 1: EARLY OPERATIVE EVIDENCE OF PERFORATION

Recoveries from perforated ulcer without operation are not rare in the surgical literature. These spontaneous recuperations, it is generally believed, are conditioned by the presence of a preformed sac of adhesions. It is assumed that the adhesions develop just prior to perforation as they do in appendicitis. Since it requires a certain amount of time for the production of delimiting membranes, perforations in which walling-off occurs are usually designated as subacute to distinguish them from the free perforations which are generally considered to be acute. The clinical history of prodromes (inaugural symptoms of Moynihan⁵), which frequently usher in the manifestations of actual rupture in cases of spontaneous recovery, is generally assumed to correspond to a preperforative stage, during which time the adhesions form.

The conception of subacute perforation as previously described is, however, not supported by an unprejudiced analysis of the facts. In the first place, pathologico-anatomic evidence to support the idea of a true subacute perforation is lacking. Recent, delimiting adhesions which are older than the perforation have been neither demonstrated to me by my surgical colleagues nor described in reports in the literature so far as I can ascertain. If they occur, they do so exceptionally. The exudate and its products in all the cases I have had the opportunity to observe, unless due to a previous rupture, are more recent than the perforation. What determines the limitation of degree and extent of the peritoneal soiling is not the presence of a preformed sac but the early spontaneous closure of the perforation. A frequent phenomenon which restricts the escape of gastroduodenal content into the free abdominal cavity is, as pointed out by Schnitzler,⁶ the covering of the hole by an adjacent

5. Moynihan, B. G. A.: *Duodenal Ulcer*, ed. 2, Philadelphia, W. B. Saunders Company, 1912.

6. Schnitzler, J.: *Ueber gedeckte Magenperforationen und über die Entstehung der penetrierenden Magengeschwüre*, *Med. Klin.* 1:938, 1912.

structure, particularly the liver. Sealing the leak by plastic exudate, plugging the hole by omentum (Moynihan⁵) and obturation by food particles are other methods which nature employs singly or in combination to effect a spontaneous cure. From the clinical standpoint, the foundation for the present notion of subacute perforation is likewise weak. Premonitory symptoms, which are said to be characteristic of a slow type of perforation, are not infrequently absent in cases in which recovery occurs spontaneously. Further, if careful inquiry is made, one is able to elicit prodromal symptoms quite frequently in the so-called acute perforations. As a matter of fact, the mode of onset in the two types of perforation is practically indistinguishable, and it is only the mild course which follows rupture in the "subacute" group which permits differentiation.

If one accepts the view that the cases formerly classified as subacute are actually acute perforations in which the hole in the stomach or duodenum becomes spontaneously sealed, then the number of cases of rupture into the free abdominal cavity, as corroborated by operation, in which spontaneous cure occurs can no longer be considered small. Lund,⁷ in 1905, reported three cases of spontaneous closure of perforations which he encountered within less than one year. At the time of operation, undertaken a few days after rupture, the perforation in each case was no longer patent. In 1907, Moynihan⁸ reported five cases in which he observed spontaneous closure at laparotomy performed at an early stage following rupture. Schnitzler⁹ reported the cases of four patients operated on by him within a period of two years, the perforation in each case being covered by an adjacent viscus. Two cases were observed by Finsterer⁹ and several were seen by Aigrot.¹⁰ Case reports in the literature intended for other purposes furnish further examples of spontaneous closure of perforated ulcer demonstrated at the operating table. For example, Kellogg,¹¹ in reporting a case of spontaneous pneumoperitoneum due to a perforated peptic ulcer, mentioned the circumstance that at the time of operation the hole

7. Lund, F. B.: Subacute Perforation of the Stomach: Report of Three Cases, Boston M. & S. J. **152**:516, 1905.

8. Moynihan, B. G. A.: Subacute Perforation of the Stomach and Duodenum, Am. Surg. **45**:223, 1907.

9. Finsterer, H.: Geheilte Fall von Ulcus duodeni Perforation, Wien. klin. Wchnschr. **28**:1240, 1915; Gedeckte Duodenalperforation, Zentralbl. f. Chir. **49**:1013, 1920.

10. Aigrot, G.: De l'obturation spontanée de certaines perforations d'estomac en peritoine libre, Presse méd. **35**:35, 1927.

11. Kellogg, W. A.: Spontaneous Pneumoperitoneum Demonstrated by the X-Ray in Acute Gastro-Intestinal Perforations, New York State J. Med. **114**:294, 1921.

was plugged by a piece of omental fat preventing the further escape of gastric content. Another case of pneumoperitoneum is reported by du Pasquier¹² in which it was recorded in the operative report that the leak in the duodenum had been checked by fibrin and omentum.

Surgical demonstration of spontaneous recovery following free perforation is not limited to the cases in which the plugged or sealed hole is directly observed, but includes also a number of ruptured ulcers in which the surgeon fails to bring the site of perforation into view. Two such groups of cases can be mentioned, the one in which the stomach and the duodenum are explored and the rupture not discovered, and the other in which the upper abdominal organs are not visualized during the course of the laparotomy. In both groups, the presence in the peritoneal cavity of a nonodorous, thin fluid resembling gastric or duodenal contents practically establishes the diagnosis of a perforated ulcer. It is not surprising that a surgeon occasionally fails to disclose a perforation, even though the incision for the exposure of the stomach and duodenum is a suitable one. At the time operation is performed, the hole is not infrequently covered, sealed or plugged, and it is necessary to reopen the hole in order to locate it. The first case of ruptured ulcer I saw in a woman was one in which there was a large quantity of characteristic fluid free in the peritoneal cavity, and yet the surgeon, even after careful exploration of the stomach and duodenum, was unable to find the site of perforation. The drain which was inserted was virtually useless, since practically nothing escaped. The unexpected recovery was astonishingly smooth. Another example of failure to isolate the perforation is summarized in case 4. These and similar cases can reasonably be considered instances of spontaneous recuperation, since operation under these circumstances frequently does nothing but add insult to injury. The drain placed in the region of the stomach accomplishes practically nothing, since the peritonitis is already diffuse and the exudate tends to gravitate to the dependent portions of the abdominal cavity.

The cases of spontaneous recovery from perforated ulcer in which the stomach and duodenum are not exposed at operation are, as a rule, those in which a mistaken clinical and pathologic diagnosis, usually of appendicitis, is made. The fluid erroneously considered appendical exudate is removed, the appendix is amputated and the upper part of the abdomen is not even explored by the unsuspecting surgeon. An instance of this not uncommon mistake is recorded in case 5, and one is related by Wickbom.¹³ These errors are rarely reported; neverthe-

12. Du Pasquier, G.: Sur un signe radiologique des perforations d'ulcérés gastriques ou duodénaux, *Rev. méd. de la Suisse Rom.* **48**:785, 1928.

13. Wickbom, H.: Ist ein sofortiger operativer Eingriff bei perforiertem Magengeschwür stets Notwendig? *Acta chir. Scandinav.* **64**:43, 1928.

less, but few hospitals of any size lack at least several examples in their history files. Perforations in which closure is difficult but in which tamponading is employed, as recommended by Hoffman,¹⁴ cannot be included as instances of spontaneous recovery from rupture attested to by early operation, but indicate the ability of the adjacent structures to seal a leak in the upper part of the gastro-intestinal tract.

CASE 1.—G. J., a colored man, aged 49, admitted to the hospital on Aug. 20, 1928, complained of periodic distress of an ulcerous type of one year's duration. Roentgen examination on the morning of August 30, entailed considerable manipulation of the stomach in an attempt to overcome a pyloric obstruction. That evening, intolerable epigastric pain developed shortly after which vomiting and hiccup occurred. The right upper abdominal quadrant was rigid and tender. Morphine afforded relief. Slight fever and a leukocytosis of 16,000 developed the next day, followed by rapid subsidence of symptoms and signs. Operation performed on September 15 disclosed a perforation of the pylorus securely covered over by the gallbladder, which formed the floor of the ulcer. The texture of the adhesions corresponded to the age of the acute pain experienced sixteen days prior. The perforation was sutured and cholecystectomy and gastro-enterostomy performed. The patient recovered.

CASE 2.—F. G., a white man, aged 47, was admitted to the hospital on Oct. 13, 1928, with a typical picture of a perforation which occurred sixteen hours previous to entrance. Laparotomy revealed free air and a moderate amount of thin fluid. The pyloric region was densely indurated and covered by thick fibrinous exudate. The site of perforation was not found. Gastro-enterostomy was performed, and a single drain inserted. There was practically no drainage from the wound. Complete recovery followed.

CASE 3.—J. N., a white man, aged 49, was admitted to the hospital on Dec. 26, 1928, with the clinical picture of a perforated ulcer. During the week prior to the development of the acute symptoms, there was an aggravation of the previous, mild symptoms of ulcer. Laparotomy performed about twenty-four hours after onset showed duodenal contents in the abdominal cavity and the liver, gallbladder and omentum bound to the duodenum by fibrinous adhesions to form one large mass. Sudden collapse of the patient led to a hasty closure without an attempt to isolate and suture the opening. After a stormy convalescence, the patient recovered completely.

CASE 4.—J. D., a white man, aged 30, entered the hospital on Jan. 13, 1929, thirty-six hours after he was seized by severe epigastric pain. There was only slight rigidity and moderate tenderness over the right side of the abdomen. Perforated ulcer was not diagnosed. At operation, performed on January 18, a week after onset, the pyloric portion of stomach was found attached to the abdominal wall by organizing adhesions which were readily torn. Separation exposed a defect of the gastric wall about which was an area of induration. The perforation was closed and gastro-enterostomy performed. The patient recovered.

CASE 5.—H. S., a colored man, aged 40, was admitted to the hospital on March 22, 1929, four hours after the onset of a most agonizing epigastric pain. The

14. Hoffman, A.: Zur Behandlung des perforierten Duodenalgeschwürs, Zentralbl. f. Chir. 38:1625, 1911.

history, symptoms and signs were typical of perforated peptic ulcer. Through an upper abdominal incision, the stomach and duodenum were explored but no perforation found. There was a moderate amount of free fluid. The appendix was thought to be phlegmonous, and it was therefore amputated. A stab wound was made over McBurney's point, and a drain was inserted. The fluid obtained at the operation had the characteristics of escaped gastric contents (particles of food). The appendix microscopically showed the inflammation to be limited to the serosa. Slow but progressive improvement followed until intercurrent erysipelas resulted in death. Autopsy was not permitted.

GROUP 2: LATE OPERATIVE EVIDENCE OF PERFORATION

The second group of cases includes those in which old adhesions are observed at operation performed some time after an assumed perforation occurred. In some instances, the adhesions are strictly localized about an indurated area in the stomach or duodenum, and the association between the ulcer and healed perigastritis is clear. In other cases, the adhesions are found in remote portions of the abdomen, and in these the relationship between the perforation and the adventitious bands is somewhat conjectural.

With regard to local adhesions, it is often stated that a perigastritis generally results from penetration of infectious material through the intact base of an ulcer. Although this mode of origin of peritoneal adhesions about the base of an ulcer is possible, it is from the practical standpoint quite exceptional. Schnitzler⁶ has adduced sufficient operative evidence to establish the contention that perigastric or periduodenal adhesions in general do not precede but rather follow the escape of contents through an actual perforation. If one is willing to accept the claim that a noteworthy degree of fibrous perigastritis or periduodenitis complicating a peptic ulcer indicates a previous perforation, then the number of spontaneous recoveries from perforation, demonstrated by operation performed after a lapse of time, cannot be considered small. For instance, Moynihan,⁸ in 1907, reported eight cases of marked local fibrous peritonitis observed at operation at a considerable interval after symptoms of perforation occurred. In three of these cases, an hour-glass deformity was found in two, evidences of pyloric obstruction. Wickbom¹³ observed five cases of acute perforation in which the upper abdominal operation was postponed. At laparotomy, performed within a few weeks, there were extensive adhesions in the region of the suspected perforation in each instance.

In the case of the more remote adhesions, the basis for assuming a perforated ulcer as the cause is the history of a chronic ulcer with supervening symptoms of acute perforation and the absence of any other causal factor. At times, the adhesions are so located (i. e., between liver and diaphragm) as to lead to no ill effects. At other times, the localization is such as to cause obstruction, as in case 10 of this series.

CASE 7.—J. D., a white man, aged 51, was admitted to the hospital on Feb. 8, 1929. His ailment was diagnosed as carcinoma of the stomach because of his marked loss of weight, absence of free acidity (with one Ewald meal only) and a rigid prepyloric deformity (fig. 1). A benign calloused ulcer of the pars media covered by dense omental adhesions was revealed at operation and also extensive adhesions between the stomach and liver. It was learned that the patient had been in the hospital previously. Reference to his old record indicated that he had entered on Sept. 22, 1928, five days after the onset of terrific pain which persisted until shortly before admission. Roentgen examination undertaken a few days later demonstrated a penetrating ulcer with a spastic incisura. Close questioning

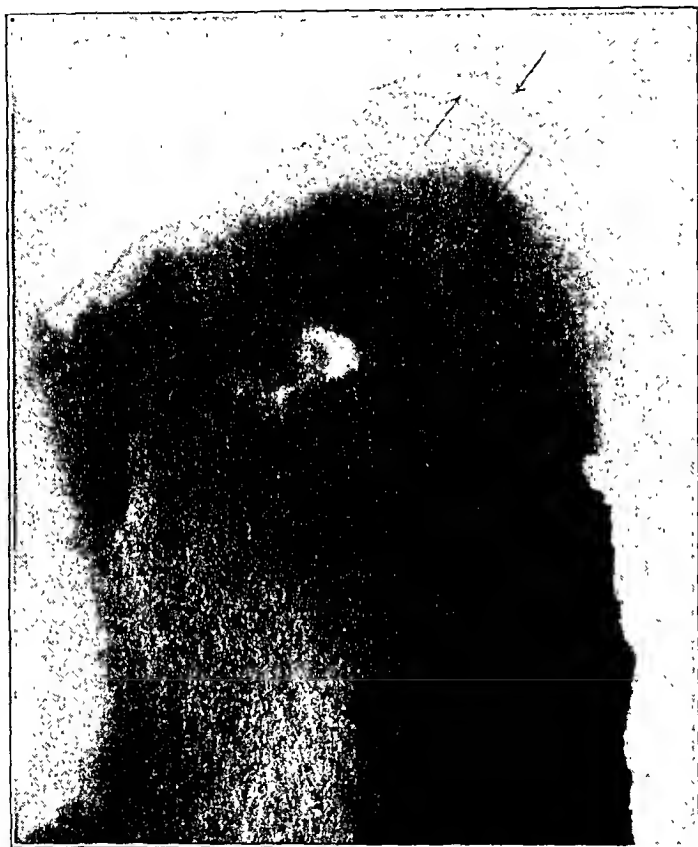


Fig. 2 (case 8).—A semilateral view taken almost five months before figure 1 and twelve days after the onset of severe abdominal pain. The arrows point to an area of radiolucence due to intraperitoneal air located between the right dome of the diaphragm and the upper surface of the liver.

yielded a clinical history typical of perforated ulcer. On reexamination of the old films, air could be discerned beneath the dome of the right side of the diaphragm (fig. 2), strong light being required to render the radiolucence apparent. The presence of a perforation indicated by the pneumoperitoneum had been overlooked during the first admission.

CASE 8.—W. B., a white man, aged 66, entered the hospital on May 16, 1929, with the symptoms, signs and roentgen indications of a duodenal ulcer and a subacute obstruction of the small intestine. An inquiry into the past history with particular reference to attacks of unusually violent pain elicited the information

that on Aug. 6, 1928, following a meal of steak and onions, the patient suffered excruciating pain, which appeared abruptly and almost annihilated him. A hypodermic injection was followed by a diminution in the intensity of the pain. After twelve hours it was no longer severe, and after twenty-four hours the pain had subsided. The patient responded to medical treatment for ulcer and entered the hospital on account of the supervention of symptoms of subacute intestinal obstruction. The patient died rather unexpectedly while under observation. Autopsy revealed an indurated duodenal ulcer attached to which was the liver and omentum. There were a number of adventitious fibrous bands, one of which had produced strangulation of a loop of ileum. No other cause for the healed peritonitis than the assumed ulcer perforation was discovered.

CASE 9.—J. L., a white man, aged 42, was admitted to the hospital on June 13, 1929, following a brisk gastro-intestinal hemorrhage. Operation on June 20 disclosed an intimate adherence of the duodenum to the gallbladder together with numerous adhesions about the pyloric portion of the stomach. After separation was accomplished, the wall of the gallbladder was found to form the base of a calloused duodenal ulcer. An antecedent perforation, closed by apposition of the gallbladder, was presumed, and the patient questioned later with this in mind. He related that in 1922, for a few days prior to Christmas he suffered from symptoms of ulcer of an aggravated character. On December 26, while driving a wagon, he was seized with excruciating knifelike pains located in the upper part of the abdomen and passing to the back. He managed to reach home with extreme difficulty half an hour later, but he was so prostrate that it was necessary to carry him into the house. One hypodermic injection administered by a physician had little effect. A gradual abatement of pain occurred during the course of the next eight days, although excruciating pain appeared with change of position during this time.

CASE 10.—J. B., a well preserved white man, aged 78, admitted to the hospital on July 5, 1929, gave a history of distress of an ulcerous character of at least three years' duration. He said that on the morning of entrance, while riding in an automobile before breakfast, he was seized by an intense, knotlike, epigastric pain which within five minutes became almost intolerable. He was rushed to the nearest physician. When he reached the hospital about six hours later, the pain had been relieved. There was moderate tenderness and rigidity in the upper right quadrant of the abdomen. On Sippy management, the patient developed a progressive pyloric obstruction which necessitated surgical intervention. Laparotomy, performed on August 5, showed the duodenum covered by dense adhesions. An attempt to separate these resulted in the exposure of a defect located in the center of an indurated area, apparently a calloused duodenal ulcer.

GROUP 3: ROENTGENOLOGIC EVIDENCE OF PERFORATION (SPONTANEOUS PNEUMOPERITONEUM)

Although I had been led to believe from observations at the operating table that spontaneous recovery was not as rare as generally believed, it was not until I became acquainted with fluoroscopic observations in cases of acute upper abdominal pain that it became apparent that recovery from free perforation without operation was not at all uncommon. In a certain number of patients in whom spontaneous pneumoperitoneum was found, it was observed that at the time of entrance the severe initial symptoms had abated and the patients were no longer

seriously ill. A number of these persons entered for diagnosis or to convalesce, and although urged, refused to submit to operation. They apparently exercised good judgment, as they made speedy and complete recoveries. It soon became apparent that spontaneous closure of the perforation had occurred in some of these cases, and at the time of admission operation was no longer indicated.

In a search through the literature dealing with pneumoperitoneum following perforated peptic ulcer, several cases are found in which spontaneous recovery occurred (Assmann,¹⁵ Ayerza and co-workers,¹⁶ Copher,¹⁷ Kellogg,¹¹ Kudlek,¹⁸ du Pasquier,¹² Popper,¹⁹ Schottmüller,²⁰ Wieland²¹). In a majority of these cases the frank admission is made that ruptured ulcer was not suspected until the roentgen examination disclosed accidentally the presence of free air. In some, operation was performed only to reveal that the perforation had been securely closed spontaneously. The case of Martin,²² which presented conflicting abdominal and pulmonary signs, is interesting. Roentgenograms taken with the idea of demonstrating pneumonia showed what was interpreted by the roentgenologist, LeWald, to be free air in the peritoneal cavity. An ulcer was subsequently demonstrated.

CASE 11.—T. O., a white man, aged 68, admitted to the hospital on April 4, 1928, said that two weeks prior he experienced sharp, shooting pain in the upper part of the abdomen. The sharp pain became replaced by a constant soreness which was present at the time of entrance. He had perspired freely the previous night, and had had one chill the morning of admission. The temperature on entrance was 102 F. There was a history of intermittent attacks of mild epigastric distress characteristic of ulcer. A clinical diagnosis of subphrenic abscess was made. Roentgen examination showed a fluid level beneath the right dome of the diaphragm. With the barium sulphate meal, the duodenal bulb was seen to be defective. Subsequent roentgen examinations showed a gradual absorption of both the fluid and the air. The patient was discharged on May 28, apparently fully recovered.

15. Assmann, H.: *Klinische Roentgendiagnostik der inneren Erkrankungen*, ed. 3, Leipzig, 1924, pp. 715-718.

16. Ayerza, L.; Espinola, R., and y Squirru, C. M.: *Neumoperitoneo espontaneo, por fisuración de una úlcera del duodeno*, *Semana méd.* **34**:1657, 1927.

17. Copher, G. H.: *Demonstration of Spontaneous Pneumoperitoneum by the Roentgen Ray (An Aid in the Diagnosis of Acute Perforating Peptic Ulcer)*, *J. A. M. A.* **82**:781 (March 8) 1924.

18. Kudlek, F.: *Zur Diagnose des durchgebrochenen Magengeschwürs*, *Zentralbl. f. Chir.* **56**:1293, 1929.

19. Popper, H.: *Die Diagnose der Darmperforation mit Hilfe der Röntgendurchleuchtung*, *Deutsche med. Wchnschr.* **49**:1034, 1915.

20. Schottmüller, H.: *Pneumothorax subphrenicus Infolge Ulcus ventriculi perforatum*, *Deutsche med. Wchnschr.* **47**:892, 1921.

21. Wieland, W.: *Ein röntgenologisches Phänomen bei perforiertem Magengeschwür*, *München. med. Wchnschr.* **62**:537, 1915.

22. Martin, W.: *Subacute Duodenal Perforation*, *Ann. Surg.* **65**:773, 1917.

CASE 13.—T. M., a strapping young white man, aged 24, admitted to the hospital on March 12, 1929, said that five hours previously he was suddenly seized by a most atrocious pain which caused him to double up and roll about. He was given two hypodermic injections by a physician with only partial relief until the time of entrance. There was a history of intermittent attacks of ulcer pain occurring over a period of a year, recently aggravated and associated with an

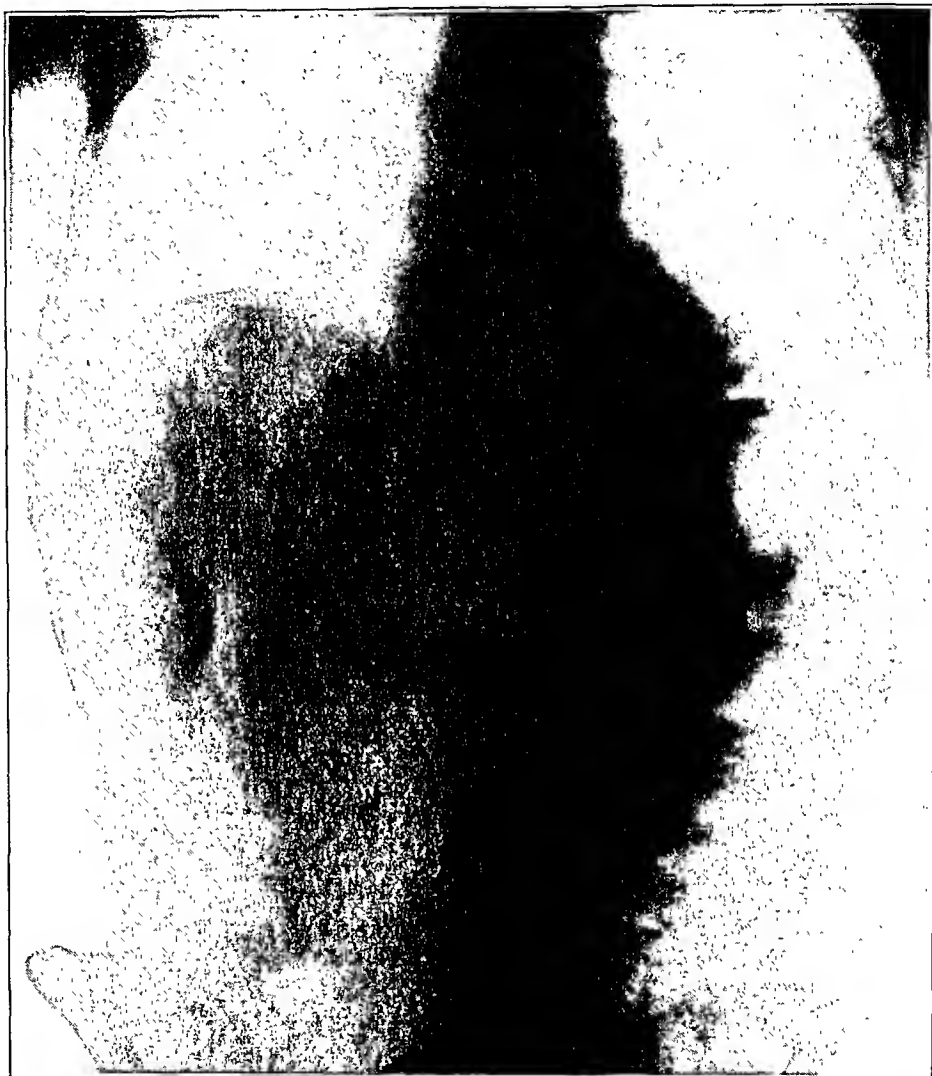


Fig. 4 (case 14).—Roentgenogram taken four days after figure 3 and eleven days after perforation. The free air has been completely absorbed.

upward pressure. The symptoms and signs on admission were those of a mild peritonitis localized to the right upper quadrant. The general condition of the patient was excellent. A diagnosis of perforated ulcer with trifling leakage was made. Fluoroscopic examination demonstrated a small intraperitoneal air bubble. Spontaneous improvement was rapid. Examination after the ingestion of a barium meal on March 22 showed a universally deformed bulb. The patient was discharged free from symptoms.

roentgen observations on a large series of perforated ulcers. Kudlek stated that in twenty-four cases of ruptured ulcer examined roentgenologically twenty showed the presence of free air. In two of the four cases lacking pneumoperitoneum, laparotomy was immediately

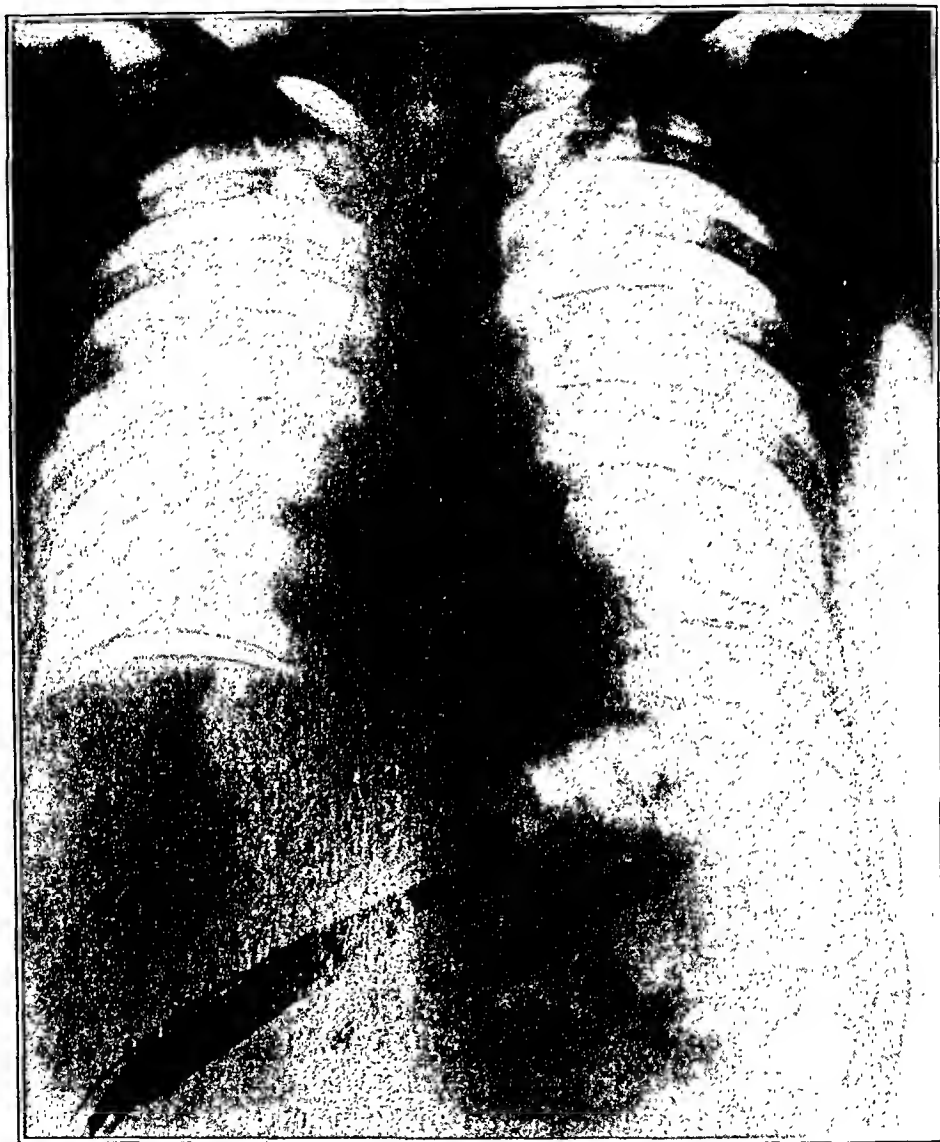


Fig. 5 (case 15).—Roentgenogram taken five days after perforation. There is free air beneath both domes of the diaphragm and considerable gas in the splenic flexure. No operation.

resorted to, and in each case a perforation covered by omental fat was found. In the other two cases, operation was not performed on account of the relative mildness of the symptoms. Although both roentgen and operative confirmation of a perforation is lacking, Kudlek made no attempt to justify or prove the correctness of his diagnosis. He appar-

least indefinite. In every case in this group, other causes of acute upper abdominal pain besides ulcer were considered in the diagnosis, and where indicated appropriate methods of examination were instituted.

CASE 16.—J. B., a white man, aged 31, admitted to the hospital on Jan. 19, 1929, had noted occasional heart-burn for many years. For four days prior to entrance, shooting pain appeared in the right upper part of the abdomen radiating to the chest. At 10 a. m. on the day of admission, the patient was suddenly stricken with severe epigastric pain which soon became generalized. A hypodermic injection administered by a private physician relieved the patient of the intense suffering, although pain on deep respiration persisted. When admitted ten hours after onset, the patient presented a tender, diffusely rigid and retracted abdomen. The peristaltic sounds were diminished. Twenty-four hours after onset, the physical signs of peritonitis were limited to the right upper quadrant. Thirty-six hours after presumed perforation, the patient was ambulatory and desired to be discharged. There was slight residual tenderness at that time. Barium meal studies undertaken on January 25 disclosed a deformed bulb. Ulcer distress occurred during a four day period early in February. By means of alkalis and restriction of diet, the patient was rendered free from symptoms.

CASE 17.—C. O., a white man, aged 35, was admitted to the hospital on Jan. 19, 1929, with the statement that six hours prior he experienced epigastric pain of such extreme intensity that he was forced to writhe on the floor. Within half an hour after onset, a physician was called who administered a hypodermic injection which failed to afford relief. There was an antecedent history of melena and periodic attacks of chronic ulcer distress, the last attack appearing in aggravated form three days before the onset of acute pain. On entrance, there were physical evidences of peritonitis localized to the right hypochondrium and to the region of McBurney's point. The temperature was 100 F. The pain continued to be severe for twenty-four hours but disappeared five days after admission. The last rise in temperature (99.2 F.) occurred the following day. On February 8, with the aid of a barium meal, a deformed duodenal bulb was demonstrated. Except for heart-burn precipitated by dietary indiscretions, the patient became free from symptoms.

CASE 18.—G. M., a heavy-set, somewhat obese white man, aged 43, was admitted to the hospital on Jan. 23, 1929, with a history of postprandial upper abdominal pain of one month's duration. Gallbladder disease had been diagnosed. Three days before admission, he was suddenly attacked by an excruciating pain in the right hypochondrium which caused him to double up and beads of perspiration to appear and rendered his abdomen as "hard as a board." During the first twenty-four hours, even morphine failed to allay the suffering. When the patient was admitted the area over the right side of the abdomen was quite tender and moderately rigid. The temperature was 100.4 F. During the period of observation, right hypochondriac pain of a relatively mild type followed the ingestion of heavier foods. Aspiration at the height of the pain showed consistently the presence of an adequate acidity. There was practically immediate relief from aspiration and from alkalis used for test purposes. Examination of the stools while the patient was on a meat-free diet gave a persistently positive Weber reaction. Roentgen examination revealed a penetrating ulcer of the stomach. The Graham-Cole test showed a gallbladder of normal contour with no evidence of stones. The emptying time was normal. On Sippy management, all abdominal symptoms vanished.

which to characterize these cases. In the second place, the recognition of perforated ulcer is not always a simple matter when all types are considered. Most of the foregoing cases were not correctly diagnosed by the original examiners. Moynihan²⁶ confessed that in eighteen of forty-nine cases which proved to be perforated ulcers he made a right lower quadrant appendical incision. Difficulty in diagnosis is encountered, especially in the *formes frustes* cases, which generally result in recovery without operation.

Only those cases which furnished evidence sufficient to satisfy the more skeptical were included in this report as instances of spontaneous recovery from perforated peptic ulcer. In addition to these forty cases, there were a number of others encountered during the course of the study in which perforation might be suspected. Noteworthy among these additional cases is a class in which the clinical picture of perforation is typical but in which operation is not performed, free air is lacking and subsequent barium studies fail to demonstrate indications of ulcer. The essential difference between this class and group 4 is the absence of roentgenologically demonstrable ulcers in the former. The class of cases in which perforation is followed by intra-abdominal suppuration which requires surgical intervention at some time cannot be rightly listed in the category of recovery without operation. Where drainage of a subphrenic or perigastric abscess is not required, as in case 11, one can justifiably speak of a spontaneous recovery.

The importance of the history can hardly be sufficiently emphasized. Unless the patient is seen early, with few exceptions, the diagnosis cannot be made without an adequate history. Even if the patient is observed within a limited period after onset, unless a satisfactory anamnesis is obtained it is difficult to arrive at a correct diagnosis. It is often necessary to suspect the presence of a perforation in order to choose the questions which yield a pertinent history. As a matter of fact, in more than a majority of spontaneous recoveries in this series the patient's story as recorded by the intern bore little resemblance to the characteristic history obtained after the diagnosis of perforated ulcer was entertained.

The mistake is often made of listing categorically the individual symptoms of which the patient complains and elaborating on the characteristics of each one. What is most essential for the diagnosis of acute perforation is a minute to minute chronological description of the onset and the subsequent few hours. In eliciting the mode of onset and early course, it is of extreme importance to have the patient narrate not only what he felt but also what action he took. For

26. Moynihan, B.: *Abdominal Operations*, ed. 4, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 234.

SUMMARY

It has been almost universally agreed that when a peptic ulcer perforates into the free abdominal cavity the outcome is practically always fatal. This view has been so deeply impressed on the minds of the medical profession that when a patient recovers from a perforated ulcer it is usually thought that the rupture occurred into a preformed sac. The conception of perforation into a walled-off sac in cases of spontaneous recovery is contradicted by the presence fluoroscopically of freely movable intraperitoneal gas and by the absence of antecedent adhesions in cases in which laparotomy is performed. The adhesions encountered follow rather than precede the actual rupture. In other words, recovery from perforated ulcer without operation is conditioned not by preformed adhesions but by the sealing, plugging or covering of the hole after rupture into the free peritoneal cavity has already occurred.

Within a period of eighteen months, forty cases of spontaneous recovery from perforated ulcer have been collected from the medical and surgical wards in the Cook County Hospital. These cases can be conveniently divided according to the nature of the evidence of perforation into four groups: (1) cases in which operation undertaken shortly after the symptoms and signs of perforation appear show the fresh rupture; (2) cases with an antecedent history of chronic ulcer and of symptoms of perforation in which, after a lapse of time, adhesions presumably due to a perforated ulcer are demonstrated; (3) cases in which a history of ulcer and symptoms and signs of perforative peritonitis are associated with the presence of spontaneous pneumoperitoneum; (4) cases in which there is a history of chronic ulcer, symptoms and signs of a perforation and the presence in a barium study undertaken after a safe interval, of an ulcer deformity. Twenty representative case reports, five from each group, chosen to illustrate the most diverse types, are described in some detail.

The general belief that practically all cases of perforated peptic ulcer pursue a typical, progressive course is not borne out by a review of the case reports. Following the symptoms of onset, the clinical manifestations in many cases rapidly subside, and complete recovery ensues within from one to several days. These are "formes frustes" cases in which limited leakage occurs because the hole becomes spontaneously closed shortly after rupture takes place.

The universal statement that perforation of a peptic ulcer into the free abdominal cavity is readily recognized is also at variance with the impression gained by reading the details of the cases herein reported. In typical cases, the diagnosis is more or less obvious. How-

THROMBO-ANGIITIS OBLITERANS (BUERGER)

IV. REDUCTION OF BLOOD VOLUME*

S. SILBERT, M.D.

A. L. KORNZWEIG, M.D.

AND

MAE FRIEDLANDER, PH.D.

NEW YORK

The high hemoglobin percentage and increased viscosity¹ that have been observed in patients with thrombo-angiitis obliterans for many years suggested the probability that in this disease there was concentration of the blood. Studies of blood volume begun several years ago by one of us tended to confirm this supposition, but the number of cases available for study at that time was too few to permit a definite conclusion to be drawn. The large number of patients with thrombo-angiitis obliterans who have been drawn to the special clinic established for this disease in the outpatient department of Mount Sinai Hospital has made available the clinical material for a more comprehensive study. From the data collected certain conclusions can now be drawn. This paper will deal only with the question of the amount of total blood and plasma in this disease.

TECHNIC

The dye method for determining the blood volume was used.² Ten cubic centimeters of blood was withdrawn; through the same needle 10 cc. of 1 per cent solution of congo red or vital red was injected. The patient was exercised to get as complete a distribution of the dye as possible. At the end of four minutes, 10 cc. of blood was withdrawn from the vein of the opposite arm. The two specimens were centrifugated at high speed (3,000 revolutions per minute) in calibrated, corked, centrifuge tubes for one hour. The exact level of cells and plasma was noted, and this was used as the hematocrit reading. The average of the two hematocrit readings was taken. The supernatant plasma was drawn off with a bulb pipet and put into clean test tubes.

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* From the Out-Patient Department and the Laboratories of the Mount Sinai Hospital.

* This work was aided by a grant from the Samuel Kellar Jacobs Research Fund for Thrombo-Angiitis Obliterans.

1. Mayesima, T.: *Klinische und experimentelle Untersuchungen über die Viskosität des Blutes*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:413, 1912.

2. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: *A Method for the Determination of Plasma and Blood Volume*, Arch. Int. Med. **16**:547 (Oct.) 1915.

The standard in each case was prepared by the dilution of 5 cc. of the same dye used for the patient with 500 cc. of distilled water in a volumetric flask. The same needle and syringe that were used for the injection of the dye into the circulation of the patient were used in this procedure in order to avoid any error due to different calibration of the syringe. The standard then had a dilution of dye equivalent to 1 cc. in 100, or 10 cc. in 1,000.

The dilution of dye in the dyed plasma was determined in a Meyer's colorimeter. Into one tube 0.5 cc. of standard solution and 0.5 cc. of normal plasma were added. Into the other tube 0.5 cc. of dyed plasma was added to 0.5 cc. of distilled water. The colors were compared. The standard was diluted until the colors matched, a solution of equal parts of normal plasma and distilled water being used as a diluent. The dilution was done with a graduated pipet, each cubic centimeter or fraction thereof being carefully noted. The original standard had a dilution equivalent to 10 cc. of dye in 1,000 cc. of solution. As used in the colorimeter, the dilution is doubled, or 10 cc. in 2,000 cc. of solution. For each cubic centimeter of diluent added, the dilution of the dye is increased by 2,000 cc. When the colors matched and the dilution was determined, the plasma volume was found by dividing the results in half.

The total blood volume was determined by the use of the hematocrit and the following ratio:

$$\frac{\text{Per Cent of Plasma}}{100\%} :: \frac{\text{Volume of Plasma}}{\times (\text{total volume})}$$

The following is an illustration of the determination of the total blood volume:

1.2 cc. of diluent used to bring standard color up to unknown.

The dilution was raised from 1/2,000 to 1/4,400.

Plasma volume was $4,400 \div 2 = 2,200$ cc.

The hematocrit was 45 per cent cells and 55 per cent plasma, therefore
 $55\% = 2,200$ cc.

$$\frac{100\%}{55} \times 2,200 = 4,000 \text{ cc.}$$

Total blood volume was 4,000 cc.

The volume of the blood and plasma per kilogram of weight of the patient was readily estimated. The greatest care was used to make the technic uniform and as faultless as possible. Determinations were made in the early morning on a fasting stomach. To avoid hemolysis, syringes, needles and graduated centrifuge tubes were washed in physiologic solution of sodium chloride before being used. If infiltration of dye outside the patient's vein took place, the test was at once abandoned. The needle and syringe were fitted perfectly so that no dye was lost at the time of injection. Patients were exercised to insure a proper distribution of dye in the body. To prevent coagulation of the blood, 0.1 cc. of a 20 per cent solution of potassium oxalate was added to the graduated centrifuge tubes. This is strong enough to prevent clotting. The blood and oxalate were mixed thoroughly but carefully by inverting the tubes twice, the thumb being held over the opening. While centrifugation was taking place, the test tubes were corked to prevent evaporation. The colorimeter tubes were cleaned with alcohol and ether and thoroughly dried. The solution of congo or vital red was prepared by dissolving the powdered dye in triply distilled water. The solution was boiled and filtered twice and sealed in glass ampules which were then sterilized in the autoclave. As the technic improved with experience, several of the earliest deter-

minations were repeated, and the second result was used. When it was impossible to recall the patient, the earlier tests were discarded. When repeated, we used a different dye so as to prevent the nonspecific immunity reaction to the original dye which some workers claim will alter the final result.³

MATERIAL STUDIED

The cases studied are divided into groups according to the following classifications:

Group I.—Patients with typical cases of thrombo-angiitis obliterans, untreated, who are still smoking. The onset of symptoms occurred before the age of 45; clearcut physical signs are present.

Group II.—Similar to group I, but the patients have been treated by intravenous injections of hypertonic sodium chloride. Most of the patients have stopped smoking.

Group III.—Borderline cases of thrombo-angiitis obliterans. The onset is between the ages of 45 and 50. The involvement is much more extensive in one lower extremity. There is no history of diabetes. No calcification is found on roentgen examination.

Group IV.—Patients temporarily classed as having thrombo-angiitis obliterans, but the symptoms and physical signs are not typical. Early onset and usually mild involvement occur.

Group V.—Atherosclerosis. The onset occurs after 50; the involvement is about equal in both lower extremities; calcifications of vessels are seen on roentgen examination. There is a history of diabetes in some cases.

Group VI.—Normal persons used for control; patients with no evident vascular disease.

RESULTS

Study of the data presented reveals a striking reduction of the blood volume in the sixty-nine typical cases of thrombo-angiitis obliterans represented by the first two groups. As might be expected, the most striking figures are found in the group of untreated patients. Here the average blood volume per kilogram is 64.3 cc., a reduction of 22.3 per cent from our normal average. The treated patients also show a similarly reduced volume, which is slightly less than that for the untreated group. It should be borne in mind that all patients who stop smoking and receive treatment gain weight. Usually the gain is from 15 to 30 pounds (6.8 to 13.6 Kg.). This would tend to make the blood volume per kilogram less, unless an actual increase in the blood volume took place. The fact that the average volume per kilogram in this group is 65.9 cc., which is somewhat higher than that for the untreated group, may be interpreted as one of the effects of treatment.

It was noted by Keith, Rowntree and Geraghty,² and also by us, that in normal persons the blood volume per kilogram tends to diminish

3. Lindhard, J.: Dye Method for Determining the Blood Volume in Man, *Am. J. Physiol.* **77**:669, 1926.

TABLE 1.—Typical Thrombo-Angiitis Obliterans (Untreated)

Name	Age	Years of Illness	Smoking	Amputation	Hemo-globin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
H. R.	44	10½	+++	1	122	3,710	81.8	3,956	2,200	48.3	26.8	44.4	55.6
R. Z.	42	19	++++	2	105	4,400	62.2	3,107	1,750	49.9	28.0	44.9	55.1
M. G.	59	19	++++	2	140	4,990	70.0	3,600	1,800	50.9	25.4	50.0	50.0
L. E.	36	8	+++	1	116	6,310	76.8	4,142	2,125	51.9	27.6	48.7	51.3
I. R.	44	17	++++	2	120	4,410	67.2	3,571	2,000	53.1	30.0	44.0	56.0
I. R.	26	1	+++	..	100	5,970	57.2	3,225	1,750	56.3	30.5	46.2	53.8
Dr. G.	32	..	+++	..	120	85.5	4,592	2,600	58.5	30.4	47.5	52.5
H. G.	44	½	++++	..	80	4,440	58.1	3,420	2,100	58.8	37.8	38.6	61.4
S. S.	41	13	++	2+	105	5,970	64.5	3,809	2,000	59.4	31.0	47.5	52.5
S. W.	48	¼	+++	..	100	4,860	73.8	4,384	2,100	59.4	28.4	47.9	52.1
D. B.	39	½	++++	..	126	5,970	69.0	4,174	2,250	60.5	32.6	46.1	53.9
S. M.	53	18	+++	2	92	5,060	47.7	2,972	1,700	62.0	35.4	42.7	57.3
J. J.	37	9	++++	2	90	6,770	67.2	4,166	2,250	62.0	33.4	46.0	54.0
A. B.	36	6	++++	1	102	6,800	62.0	4,541	2,625	73.3	42.2	42.2	57.8
A. K.	37	7	+++	2	95	5,800	4,218	2,400	62.7	35.7	43.1	56.9
A. S.	47	16	++++	2	124	5,030	66.3	4,175	1,900	63.0	28.0	51.5	48.5
A. S.	45	8	++++	2	120	4,230	46.3	2,949	1,700	63.4	36.7	42.8	57.2
A. K.	60	15	+++	2	105	5,360	68.0	4,326	2,250	63.6	33.5	47.3	52.7
M. G.	40	8	++++	..	102	5,550	67.5	4,371	2,400	64.7	35.5	45.1	54.9
M. L.	37	5	++	1	92	6,040	56.0	3,682	2,125	65.0	36.9	42.3	57.7
S. M.	44	16	++++	..	105	6,130	71.5	4,665	2,500	66.2	36.9	46.4	53.6
S. D.	34	1½	+++	1	115	6,350	43.6	2,850	1,500	65.3	31.8	47.5	52.5
O. L.	21	4	+++	..	105	6,080	67.3	4,494	2,400	66.7	35.6	46.6	53.4
C. H.	40	2	++++	66.5	4,515	2,500	68.3	37.5	45.0	55.0
J. K.	40	2	++++	..	104	4,500	95.9	6,600	3,500	68.8	36.6	46.9	53.1
J. E.	36	3	+++	..	100	5,620	70.0	4,830	2,700	69.0	38.5	44.1	55.9
W. M.	40	2	+++	1	98	4,270	70.0	4,849	2,900	69.2	41.4	40.2	59.8
S. E.	45	21	++++	2	120	5,960	55.0	4,047	2,200	73.5	40.0	45.4	54.6
M. E.	34	4	+++	..	100	5,400	57.0	4,280	2,500	75.0	43.8	41.7	58.3
B. Z.	45	13	+++	2+	122	7,770	42.0	3,925	2,100	93.4	50.0	46.5	53.5
S. S.	35	10	++	1	46.3	4,409	2,500	95.2	51.0	43.3	56.7
Average										64.3			35.3

TABLE 2.—Typical Thrombo-Angiitis Obliterans (Treated)

Name	Months of Treatment	Age	Years of Illness	Smoking	Amputation	Hemo-globin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
O. de M.	11	42	1	++++	..	100	5,990	78.1	3,710	2,000	46.4	25.0	44.6	53.4
M. R.	36	50	7	+++	..	96	6,060	54.4	2,680	1,500	40.6	27.7	44.0	56.0
D. S.	3	40	12	++++	..	105	5,860	68.1	3,623	2,000	53.1	29.3	44.5	55.5
W. K.	23	33	3	++++	..	95	5,390	84.5	4,405	2,625	53.2	31.0	41.6	58.4
L. R.	36+	42	12	++++	..	108	5,990	71.0	3,800	1,900	53.5	27.8	50.0	50.0
W. S.	3	36	5½	++++	..	108	6,140	80.0	4,880	2,625	53.7	27.1	46.3	53.7
N. D.	34	38	4½	+	..	111	5,110	73.1	4,365	2,400	54.9	30.4	45.0	55.0
N. F.	36+	47	20	++++	2	102	5,580	73.1	3,657	2,135	54.9	29.0	41.9	58.1
A. S.	33	53	16	++	1	105	5,150	84.3	4,880	2,750	57.8	32.7	43.6	56.4
I. L.	29	37	4	++	..	95	4,290	79.0	4,895	2,600	58.1	33.0	43.4	56.6
L. B.	7	47	19	++++	1	102	4,980	72.7	5,942	3,500	60.8	36.1	40.9	59.1
M. G.	36+	36	9	++	1	100	4,800	67.0	4,108	2,200	61.3	32.8	46.7	53.3
W. N.	34	50	3	++++	..	125	5,440	88.0	4,200	2,100	61.7	30.8	50.0	50.0
M. K.	13	41	3	++++	1	105	6,080	83.0	5,187	2,800	61.8	33.8	45.5	54.5
H. D.	8	38	8	++	..	105	5,100	59.5	3,833	2,300	63.8	33.3	40.0	60.0
P. R.	36+	31	7	++++	1	74.5	4,639	2,700	62.2	36.2	41.8	58.2
D. L.	16	39	2	+	..	120	4,800	56.3	3,597	1,900	63.5	32.0	47.2	52.8
E. L.	16	36	3	++++	..	110	5,390	60.0	3,820	2,100	63.6	35.0	45.1	54.9
L. W.	36+	42	4½	++++	..	70	3,880	63.8	4,378	2,125	63.8	36.4	42.9	57.1
N. S.	4+	45	4	++++	..	135	5,790	66.2	4,572	2,300	65.6	36.2	49.7	50.3
F. A.	36+	38	9	++++	..	100	5,020	64.5	4,270	2,400	66.0	36.9	43.8	56.2
J. O.	1½	31	4	++++	1	116	5,010	76.3	5,078	2,600	66.5	32.7	48.8	51.2
N. D.	16	43	16	++	..	95	5,280	71.3	4,795	2,700	66.7	37.6	43.7	56.3
V. N.	16	37	2	++	..	110	5,000	64.3	4,236	2,200	66.8	34.2	48.9	51.2
S. Z.	18	42	2	++	..	104	6,050	89.3	6,000	3,300	67.2	36.9	45.0	55.0
A. R.	3	31	2½	++++	..	120	5,360	72.7	4,869	2,800	67.6	36.6	42.5	57.5
H. K.	10	34	1	++++	..	115	5,200	60.0	4,089	2,200	68.1	36.6	46.2	53.8
A. F.	12	49	11	++	1	105	4,040	60.9	4,431	2,300	73.8	38.3	48.1	51.9
R. B.	7	30	6	++++	..	97	6,010	60.9	3,952	2,100	68.2	34.4	47.1	52.9
R. B.	26	53	19	++	..	120	6,400	61.7	4,220	2,300	68.2	37.2	45.5	54.5
H. E.	30	44	23	+	..	90	5,780	91.3	6,306	3,500	69.0	38.3	44.5	55.5
E. A.	27	41	8	++++	1	100	5,020	73.6	5,504	2,900	70.0	36.9	47.5	52.5
L. F.	24	31	4	++	..	115	5,500	68.2	4,363	2,400	70.1	36.6	45.0	55.0
D. L.	20	35	5	++++	1	116	6,020	69.5	5,513	2,900	71.0	37.7	47.4	52.6
S. W.	17	36	6	++	1	98	4,440	91.3	6,688	4,000	72.9	43.5	40.2	59.8
M. H.	18	43	½	+	..	105	5,020	65.4	5,045	2,800	77.1	42.8	44.5	55.5
N. R.	21	43	14	++	..	112	5,940	70.5	6,049	3,200	83.3	44.4	47.1	52.9
W. K.	36+	44	3	++++	1	120	5,120	58.6	4,635	2,350	79.0	40.0	49.3	50.7
P. E.	36+	40	17	++++	2	110	61.0	6,143	3,600	130.7	59.0	41.4	58.6
Average.....						128	5,940	50.4	5,088	2,600	109.9	53.5	48.9	51.1
											65.9	36.4		

TABLE 3.—*Borderline Thrombo-Angiitis Obliterans*

Name	Months of Treatment	Age	Years of Illness	Smoking	Amputation	Hemo-globin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
L. W.	3	50	1/4	+++++	..	125	5,150	75.0	4,664	2,500	62.1	33.3	46.4	53.6
M. S.	13	53	4	+++++	..	105	5,270	63.0	4,545	2,500	65.0	33.4	45.0	55.0
L. K.	1	48	1	++++	67.5	4,455	2,200	66.0	32.5	50.6	49.4
H. S.	5	47	3	+++++	..	110	5,530	62.6	4,153	2,100	66.2	33.4	49.5	50.5
M. D.	7	56	7	+++++	..	120	5,440	71.6	4,860	2,600	67.8	36.3	46.5	53.5
S. O.	5	49	4	++++	..	100	4,770	69.3	4,853	2,750	69.2	39.8	43.5	56.5
B. P.	1	51	1 1/2	++++	..	140	4,230	78.1	5,630	2,900	72.1	33.3	52.6	47.4
D. G.	7	55	6	++++	1	112	5,420	61.3	4,570	2,550	74.5	41.3	44.2	55.8
B. M.	17	50	5	++++	..	93	4,670	70.0	5,463	2,950	78.0	42.1	46.0	54.0
L. J.	2	48	2 1/2	++++	..	88	4,520	61.5	4,846	2,800	79.3	45.5	41.6	58.4
J. S.	2	49	1 1/2	++++	..	100	5,010	61.8	4,905	2,700	79.3	45.3	42.9	57.1
I. S.	0	45	1	+++++	..	95	4,441	63.1	5,263	3,100	83.4	47.5	41.1	58.9
Average.....											71.8			39.0

TABLE 4.—*Atypical Thrombo-Angiitis Obliterans*

Name	Months of Treatment	Age	Years of Illness	Smoking	Hemo-globin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
E. M.	0	42	1/2	++++	116	5,930	86.3	5,416	2,925	63.3	33.8	46.0	54.0
T. C.	5	44	1/4	++++	110	6,090	77.7	5,340	2,850	68.8	38.1	46.7	53.3
I. S.	5	38	3	+++++	90	4,870	57.9	4,207	2,600	72.6	44.5	38.2	61.8
H. S.	5	40	3	++++	120	5,380	73.6	5,459	2,900	74.7	38.0	48.7	51.3
L. F.	1	33	1/4	+	115	5,860	64.1	5,165	2,650	79.5	40.7	48.7	51.3
A. W.	0	44	3	++++	105	5,440	56.5	4,930	2,500	87.2	44.2	49.3	50.7
Average.....										74.3			39.9

TABLE 5.—*Atherosclerosis*

Name	Months of Treat- ment	Age	Years of Illness	Smoking	Amputa- tion	Hemo- globin, per Cent	Red Blood Cell Count	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Blood Volume per Kg.	Plasma Volume per Kg.	Cell, per Cent	Plasma, per Cent
M. L.	21	56	5	++++	..	80	3,760	54.5	3,653	2,225	67.3	42.6	39.4	60.6
M. F.	23	51	4½	++++	..	102	4,530	75.4	5,370	2,900	75.4	39.5	46.0	54.0
P. A.	1	51	1½	+++	..	116	4,370	76.1	5,936	3,200	78.0	42.0	46.1	53.9
H. McG.	13	55	2	+++	..	104	4,720	68.0	5,400	2,914	79.0	42.0	46.0	54.0
A. R. *	1	71	?	++++	1	64.0	5,087	2,900	79.5	45.3	43.0	57.0
M. C.	0	59	2½	++++	..	102	5,230	75.9	6,078	3,100	79.9	40.7	49.0	51.0
B. S. *	0	42	?	?	51.8	2,909	2,900	83.0	57.0	32.7	67.3
L. C.	3	55	9	++++	..	120	4,080	51.3	4,400	2,200	86.1	43.0	50.0	50.0
O. K. *	0	76	?	?	51.0	5,374	2,800	94.6	49.3	47.9	52.1
Average.....											79.8			

* Diabetic patient.

TABLE 6.—*Controls*

Name	Age	Smoking	Weight, Kg.	Hemo- globin, per Cent	Red Blood Cell Count	Total Blood Volume	Total Plasma Volume	Weight, Kg.	Total Blood Volume	Total Plasma Volume	Cell, per Cent	Plasma, per Cent	Illness
J. S.	34	..	70.9	...	5,200	2,600	73.3	36.6	50.0	50.0	50.0	50.0	Ureteral calculus
S. S.	29	+	67.0	110	5,200	2,700	75.3	40.3	53.4	53.4	46.6	53.4	Ureteral calculus
L. A.	40	..	70.4	...	5,309	3,000	75.9	42.6	56.5	56.5	43.5	56.5	Hypertrophy of breast
W. B.	52	+++	68.9	...	5,263	3,000	76.3	37.7	49.4	49.4	50.6	52.0	Cut hand
J. D.	29	+++	80.0	...	5,153	3,200	76.8	40.0	50.1	50.1	49.9	50.1	Rectal ulcer
M. N.	42	..	68.1	...	5,389	2,700	78.2	30.5	56.1	56.1	43.9	56.1	Varicose veins
M. K.	45	+	75.2	110	5,450	3,300	78.2	43.8	58.1	58.1	44.1	55.9	Gastric ulcer
S. F.	27	..	63.6	...	5,068	2,800	78.5	43.7	51.7	51.7	45.6	54.4	Skin Infection
L.	48	..	63.6	...	5,024	2,800	78.9	43.5	54.4	54.4	41.6	55.9	Pneumonia
Dr. S.	26	+	62.3	95	4,940	2,750	80.0	43.0	50.9	50.9	49.4	52.4	Infected sebaceous cyst
O. N.	19	+	64.3	105	5,130	2,800	81.2	43.0	50.4	50.4	44.8	55.2	Gastric ulcer
H. H.	18	..	72.3	...	5,929	3,000	82.0	41.0	50.4	50.4	49.6	50.4	Cholecystitis
S. G.	22	+++	65.0	119	6,260	3,400	86.7	49.1	56.7	56.7	43.3	56.7	Normal
S.	42	..	56.4	...	5,715	3,500	87.0	47.0	52.4	52.4	41.5	53.5	Gastric neurosis
F. R.	41	..	74.5	...	5,894	3,450	90.0	48.0	54.3	54.3	45.7	61.2	Infected nail
S. N.	23	+++	69.0	...	5,156	2,800	90.6	53.4	53.7	53.7	43.5	56.5	Ulcer of foot
A. K.	25	+++	74.5	...	5,470	3,200	91.6	54.2	57.8	57.8	42.2		Gastric symptoms
G.	39	+	67.2	...	5,223	2,800	93.5						
J. H.	17	0	57.7	80	4,938	3,200							
A. E.	13	0	52.2	...	5,708	3,200							
A. L.	26	++	59.1	...									
G.	44									
Average.....							52.7			41.7			

as the weight increases. Study of our thrombo-angiitis obliterans cases shows a parallel tendency, even though the volume is already less (chart 1). Similar study of the influence of age on blood volume fails to show any changes due to this factor, either in normal persons² or in our group of patients with thrombo-angiitis obliterans (chart 2).

Of the group of sixty-nine cases classed as typical thrombo-angiitis obliterans, seven showed a blood volume of 75 cc. or more per kilogram. Retesting in some of these cases showed that error in technic was not responsible for these high figures. The conclusion must be drawn that about 10 per cent of cases do not show the typical reduction in blood volume. We have no explanation for this fact at the present time. If this 10 per cent is excluded, the average blood volume in the typical cases is much lower.

TABLE 7.—*Table of Averages*

Group	Number of Cases	Blood Volume per Kg.	Reduction from Normal, per Cent	Plasma Volume per Kg.	Reduction from Normal, per Cent
I. Thrombo-angiitis obliterans, typical, untreated	30	64.3	22.3	35.3	21.1
II. Thrombo-angiitis obliterans, typical, treated	39	65.9	20.4	36.4	19.6
III. Thrombo-angiitis obliterans, borderline	12	71.8	13.2	39.0	12.8
IV. Thrombo-angiitis obliterans, atypical	6	74.3	10.2	39.9	10.8
V. Atherosclerosis	9	79.8	3.6	44.2	1.2
VI. Controls (normal)	22	82.7	44.7

Group III includes patients with circulatory disease of the extremities whose symptoms began after the age of 45, but who otherwise present the characteristic features of thrombo-angiitis obliterans. They might therefore be classed as having a mild form of the disease, and it is interesting to note that the reduction in blood volume is also less striking. It is possible that owing to the slow development, compensation has taken place to a considerable extent.

In group IV, the figures for blood volume are nearly normal, 74.3 cc. per kilogram. This group of patients is included with those with thrombo-angiitis obliterans for the time being, but there is a reasonable doubt that they belong to the group. A variety of conditions may occasionally lead to some organic obstruction of the circulation, such as presenile atherosclerosis, arteritis associated with infectious diseases, thromboses resulting from trauma or other injury, etc. A few of these cases may represent mild forms of thrombo-angiitis obliterans.

Group V presents a series of cases of vascular occlusion due to another type of pathologic process, atherosclerosis. These cases were studied in order to determine whether the reduction of volume was caused by mere obliteration of the vascular area, which is present in atherosclerosis as it is in thrombo-angiitis obliterans. It is interesting

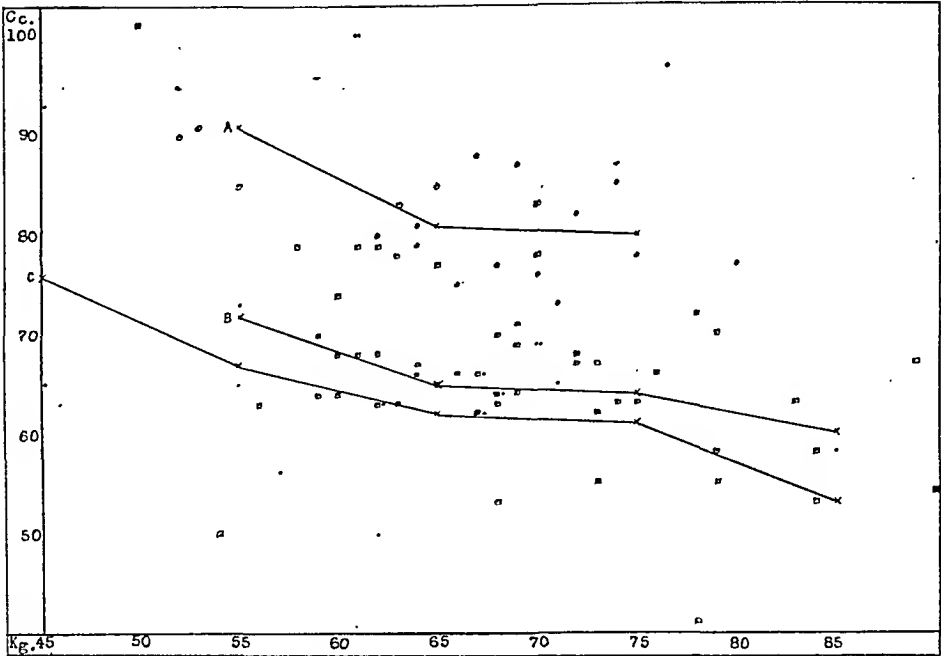


Chart 1.—Relation of weight to blood volume. *A* indicates the curve for normal persons; *B*, that for treated patients with thrombo-angiitis obliterans, and *C*, that for untreated patients with thrombo-angiitis obliterans.

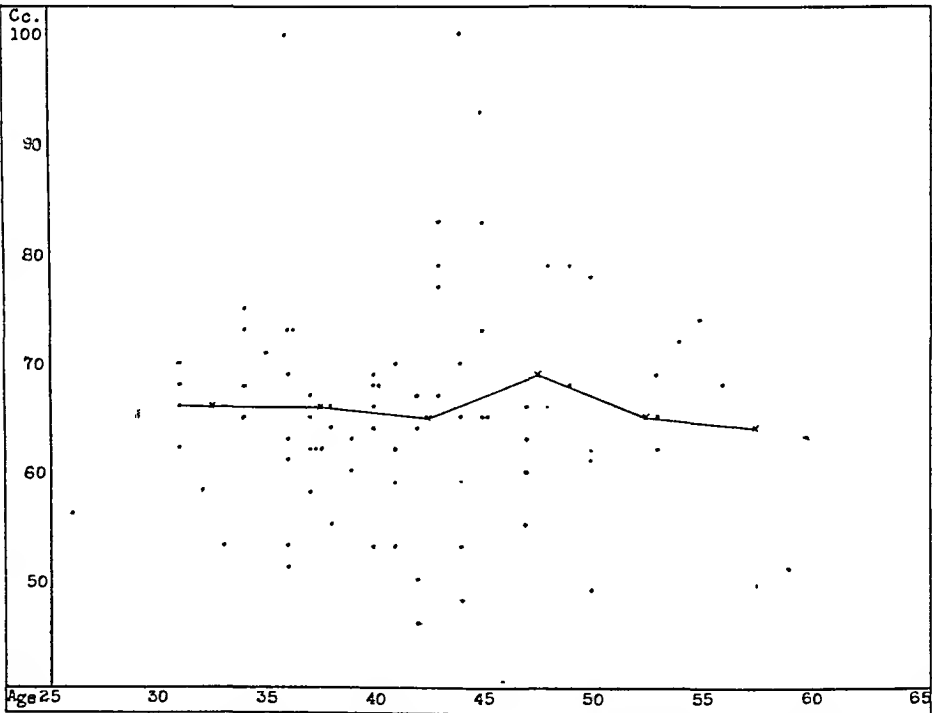


Chart 2.—Relation of age to blood volume (groups I, II and III).

to note that reduction of blood volume is not present in these cases. This fact would suggest that some factor which is part of the disease process in thrombo-angiitis obliterans is responsible for the reduction.

Finally, in group VI a series of controls establishes a normal average figure for the technic employed. This average corresponds with the figures obtained by other investigators for normal persons.²

It is noteworthy that in the cell-plasma ratio, as established by the hematocrit method, a slight tendency for a higher percentage of cells may be discerned. It is possible that the actual number of cells is nearly normal, and their apparently higher count is due to concentration in a smaller amount of plasma. Studies of the individual constituents of the plasma to determine their amount and relative proportions have been made and will be reported on later.

SUMMARY AND CONCLUSIONS

1. A study of blood volume by the dye method in eighty-seven cases of thrombo-angiitis obliterans, nine cases of atherosclerosis and twenty-two normal persons was made.

2. An average reduction of 21 per cent in blood volume was found in sixty-nine typical cases of thrombo-angiitis obliterans.

3. This fact suggests that a concentration of the blood is usually present in this disease.

THE CARDIAC OUTPUT IN HEART DISEASE

II. EFFECT OF EXERCISE ON THE CIRCULATION IN PATIENTS WITH CHRONIC RHEUMATIC VALVULAR DISEASE, SUBACUTE RHEUMATIC FEVER AND COMPLETE HEART BLOCK *

HOWARD L. ALT, M.D.

AND

GEORGE L. WALKER, M.D.

BOSTON

AND

W. CARTER SMITH, M.D.

ATLANTA, GA.

Our object in this study was to determine the effect of exercise on the cardiac output of several patients with heart disease. These patients were studied first under basal conditions, and the results were reported in paper I.¹ The group consisted of three patients with chronic rheumatic valvular disease, one with subacute rheumatic fever, one with probable "chronic myocarditis" and two with complete heart block. In addition, control observations were made on four normal subjects, one of whom was obese.

The effect of graded exercise (by means of the stationary bicycle) on the output of the heart in normal subjects has been reported by Krogh and Lindhard,^{1a} Means and Newburgh,² Boothby,³ Collett and Liljestrand,⁴ and Bock and his co-workers.⁵ The earlier workers used the nitrous oxide method to determine the cardiac output, whereas Bock's observations were made with the modified "Haldane method." The latter procedure, as described by Bock, Dill and Talbott,⁶ was used

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

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in our studies. In general, these authors have found that the cardiac output increases in direct proportion to the respiratory metabolism but that considerable variations exist in different persons at a given level of oxygen consumption.

Few observations have been reported on the output of the diseased heart during exercise. Means and Newburgh² studied the effect of exercise on the oxygen consumption and the cardiac output in a patient with double mitral and aortic disease. This patient had moderate cardiac enlargement but was able to do light work without discomfort. The reaction of this patient was similar to that of a normal subject until the amount of work exceeded 630 kilogram meters per minute; he then experienced considerable distress, whereas a normal subject could do work up to 1,040 kilogram meters per minute without difficulty. It is interesting to note that this patient complained more of general fatigue than of real dyspnea with the higher grades of exercise. Meakins, Dautrebande and Fetter⁷ studied the cardiac output in three patients with mitral stenosis immediately after mild effort. The work was very light as the carbon dioxide excretion did not exceed 200 cc. a minute, while in our observations, with the lightest grade of work, the carbon dioxide excretion averaged between 700 and 800 cc. a minute. In their cases, the cardiac output increased from a resting level of from 3 to 4 liters a minute to about 5 liters a minute after exercise. The patients experienced symptoms out of all proportion to the work done.

Lundsgaard⁸ studied two elderly patients with complete heart block. Both had previously been decompensated, and one had mitral insufficiency and auricular fibrillation. Directly following mild exercise, he found a marked increase in the coefficient of utilization (nitrous oxide method). The oxygen consumption was not measured, but from the high coefficients of utilization, he concluded that the minute circulation could not be increased appreciably. During exercise, both patients had moderate elevations in the ventricular rate (from 36 to 48 and from 40 to 46). Liljestrand and Zander⁹ studied the effect of various grades of exercise on the cardiac output of a young patient with uncomplicated complete heart block. The ventricular rate increased from an average of 50 during rest to around 100 beats a minute during heavy exercise.

7. Meakins, J.; Dautrebande, L., and Fetter, W. J.: The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: IV. The Blood Gases and the Circulation Rate in Cases of Mitral Stenosis, *Heart* **10**:153, 1923.

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The cardiac output responded normally to different grades of work, there being a minute output of 16 liters when the oxygen consumption was 1,500 cc. a minute. The stroke volume seemed to be limited at about 100 cc. No studies of the cardiac output under exercise are reported for patients with complete heart block in whom the ventricular rate did not increase with exertion.

PROCEDURE

Repeated observations were made in each subject, two standard grades of work being used. The exercise was obtained with the Krogh bicycle ergometer¹⁰ which was well adapted for the repetition of a standard amount of work. A uniform rate of 36 revolutions of the sprocket per minute was used. Every subject was able to keep the down stroke of each pedal in time with a metronome adjusted at 72 beats a minute. Two different loads were applied by means of an electromagnet. These, with the uniform rate, amounted to work of 234 and 351 kilogram meters per minute respectively, and simulated riding a bicycle on level ground and up a slight slope at the rate of about nine miles an hour. Each subject had a preliminary practice period on the bicycle, in order to acquaint him with the procedure. All observations were made either two hours after breakfast or two hours after a light lunch. Following a resting period of ten minutes on the bicycle, exercise was begun. From seven to ten minutes was allowed for the establishment of a "steady state" before the cardiac output was determined.

The method used for measuring the cardiac output during exercise has been described by Bock, Dill and Talbott.⁶ This is essentially the method of Field, Bock, Gildea and Lathrop¹¹ used in resting subjects (described in paper I), with two modifications. First, in collecting the alveolar air, the former group found that more accurate results are obtained by giving the command "blow" at the beginning of expiration instead of at the end, as is employed in resting subjects. This prevents piling up of carbon dioxide which would result in increased values. Second, in collecting the "virtual venous" sample of carbon dioxide (that which is in equilibrium with the carbon dioxide of the venous blood), the subject holds the oxygen-carbon dioxide mixture in his lungs instead of rebreathing into the bag. During the "holding period," the carbon dioxide of this mixture becomes in equilibrium with the carbon dioxide of the venous blood. The subject then expires forcibly and the sample is collected from a side arm before it reaches the rubber bag. A holding period of from nine to twelve seconds is necessary when the oxygen consumption ranges from 750 to 1,500 cc. a minute. In our studies, holding periods of ten seconds were used in every case, as the oxygen consumption averaged between 800 and 1,100 cc. a minute. A mixture of 91.5 per cent oxygen and 8.5 per cent carbon dioxide was used in the bag, as this was the approximate percentage of carbon dioxide that we found in the virtual venous samples during exercise. After the collection of each sample, from 12 to 15 cc. of carbon dioxide was added to the bag to make up for any loss sustained from dilution of the mixture with air in the dead space of the respiratory tract.

10. Krogh, A.: A Bicycle Ergometer and Respiration Apparatus for the Experimental Study of Muscular Work, *Skandin. Arch. f. Physiol.* **30**:375, 1917.

11. Field, J. H.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, *J. Clin. Investigation* **1**:65, 1924.

Four alveolar and four venous carbon dioxide samples were collected during each period of exercise according to this method. The expired air was collected in a 125 liter spirometer for two minute periods, once after the first alveolar and venous samples and again after the third. Taking the alveolar and venous carbon dioxide samples did not seem to affect the respiration or the metabolism, as spirometer periods taken just before and after these samples gave similar results. The calculations presented in table 1 show how the cardiac output was derived.

Heart rates were obtained every two to four minutes by palpation of the radial artery or by direct auscultation over the precordium, and blood pressures were recorded at the same intervals with a Tycos syphygmomanometer that was kept in place throughout the procedure. Respirations were counted by observing the

TABLE 1.—*Method of Calculating Cardiac Output (Case 4)*

No.	Alveolar Percentage of Carbon Dioxide, Mm. Hg	Venous Percentage of Carbon Dioxide, Mm. Hg	Arteriovenous Difference in Percentage of Carbon Dioxide, Mm. Hg	
1	38.6	57.5	18.9	Average arteriovenous difference *19.6 mm.
2	39.2	58.9	19.7	Slope on dissociation curve..... 0.42
3	36.4	56.4	20.0	†Carbon dioxide transport, per
4	37.2	57.0	19.8	cent by volume 8.03
Metabolism Period 1				Metabolism period 2
Oxygen.....		17.12 per cent		Oxygen..... 17.18 per cent
Carbon dioxide.....		3.67 per cent		Carbon dioxide..... 3.54 per cent
		3.64		3.51
Respiratory quotient.....		$\frac{3.64}{3.85} = 0.94$		Respiratory quotient..... $\frac{3.51}{3.81} = 0.92$
Ventilation per minute.....		26,900 cc.		Ventilation per minute..... 28,000 cc.
Oxygen consumption per minute....		1,039 cc.		Oxygen consumption per minute.... 1,067 cc.
Carbon dioxide produced per minute		982 cc.		Carbon dioxide produced per minute 933 cc.
Calculation of Cardiac Output				
Average carbon dioxide produced per minute.....				982.5 cc.
Carbon dioxide transport.....				8.03 per cent by volume
				982.5×100
Cardiac output per minute.....				$\frac{8.03}{8.03} = 12,235$ cc.

* Normal standard dissociation curves, plotted at rest and during exercise (Bock, A. V.; Field, H., Jr., and Adair, G. S.: *J. Biol. Chem.* 59:353, 1924. Bock, A. V.; Dill, D. B.; Hurxthal, L. M.; Lawrence, J. S.; Coolidge, T. G.; Dailey, M. L., and Henderson, L. J.: *Ibid.* 73:749, 1927), were employed in these experiments. The determination of individual carbon dioxide dissociation curves was thought unnecessary since all our subjects had a normal amount of hemoglobin and there was no cause for an abnormal amount of fixed base. Furthermore, Meakins and others (Meakins, Deutrebände and Fetter, footnote 6) have found that carbon dioxide dissociation curves (on arterial blood by indirect observation) are normal in patients with mitral stenosis.

† The carbon dioxide transport is decreased by 0.2 per cent by volume because the arterial blood is only 95 per cent saturated.

opening and closing of the flutter valves on the inlet tube. The total period of exercise usually lasted from twenty to twenty-five minutes. The heart rate, blood pressure and respiration were then followed until a resting level was reached.

The so-called steady state as described by Bock and his associates²² is illustrated in these studies by the relative similarity of observations made during a period of exercise. The arteriovenous carbon dioxide differences determined over an interval of from ten to fifteen minutes show even closer agreement than similar differences when taken at rest. Spirometer periods taken from five to

12. Bock, A. V.; Vancaulaert, C.; Dill, D. B.; Fölling, A., and Hurxthal, L. M.: *Studies in Muscular Activity: IV. The "Steady State" and the Respiratory Quotient During Work*, *J. Physiol.* 66:162, 1928.

TABLE 2.—*Observations in Normal Subjects and in Patients with Heart Disease at Rest and During Exercise*

Date, 1929	Work, Kilogram- Meters per Minute	Blood Pressure			Pulse Rate	Pulse Pres- sure	Respi- ration per Minute	Ventila- tion Liters per Minute	Oxygen Consump- tion per Minute, Cc.	Carbon Dioxide Expired per Minute, Cc.	Respi- ratory Quo- tient	Arteriovenous Difference in			Stroke Volume, Cc.	Comment
		Sys- tole, Mm. Hg	Diastolic, Mm. Hg	Mean, Mm. Hg								Alveolar Percent- age of Carbon Dioxide, Mm. Hg	Venous Percent- age of Carbon Dioxide, Mm. Hg	Cardiac Output, Liters per Minute		
M. F., a man, aged 29; height, 177 cm.; weight, 63 Kg.; vital capacity, 5,200 cc.; normal																
Jan. 7, p.m.	Basal	63	120	78	42	12	5.8	250	199	0.80	40.5	50.4	4.09	4.9	77	
Feb. 14	Basal	60	114	80	34	13	6.0	260	201	0.78	41.0	50.5	4.2	4.7	78	
Feb. 1, p.m.	234	119	140	75	65	18	19.9	877	840	0.96	45.4	62.8	6.76	12.4	104	
Feb. 6, p.m.	234	108	135	75	60	17	19.1	808	767	0.95	43.0	60.6	6.83	11.2	104	Slight fatigue of legs
Feb. 21, a.m.	351	122	155	80	75	18	26.3	1,205	1,105	0.92	42.3	60.6	7.48	14.8	121	
S. L., a man, aged 38; height, 171.5 cm.; weight, 60.3 Kg.; vital capacity, 4,000 cc.; normal																
Feb. 6	Basal	59	108	69	40	12	4.8	195	157	0.82	41.4	51.7	4.27	3.7	65	
Feb. 18	Basal	53	110	68	42	9	4.4	210	153	0.73	40.1	49.6	4.00	3.8	72	
Feb. 9, p.m.	234	115	145	75	70	18	19.3	775	749	0.97	38.8	59.1	8.3	9.1	79	Moderate fatigue of legs
Feb. 16, p.m.	351	142	155	75	80	19	23.1	1,060	1,006	...	41.9	62.4	8.0	12.6	89	Respiratory infection since last experi-
Mar. 2, p.m.	351	130	140	70	70	17	22.4	1,050	992	0.95	43.4	62.1	7.28	13.6	105	ment
E. H., a man, aged 27; height, 178 cm.; weight, 74.2 Kg.; vital capacity, 5,300 cc.; normal																
Jan. 5	Basal	75	128	90	38	17	5.9	248	200	0.81	44.5	51.7	2.81	7.1	95	
Jan. 12	Basal	84	130	80	50	16	6.4	264	191	0.75	42.4	48.9	2.64	7.4	88	
Jan. 31, p.m.	234	109	150	80	70	23	18.4	783	714	0.92	44.3	58.9	5.6	12.7	117	
Feb. 4, p.m.	234	103	150	75	75	23	18.9	777	770	0.99	44.9	49.0	5.44	14.2	137	
Feb. 25, a.m.	351	120	155	78	77	23	22.8	980	964	0.98	41.2	61.4	6.63	14.4	120	Head cold for five days
R. K., a man, aged 29; height, 180 cm.; weight, 95 Kg.; vital capacity, 4,200 cc.; normal (obesity)																
Feb. 14	Basal	63	120	84	36	14	9.7	304	290	0.95	35.9	46.2	4.51	6.4	102	
Feb. 16	Basal	62	118	80	38	12	8.5	299	262	0.88	33.3	44.6	5.07	5.2	83	
Feb. 7, p.m.	234	92	140	85	55	19	22.4	1,250	910	0.73	41.2	56.2	6.11	14.9	162	
Feb. 13, a.m.	234	98	145	90	55	15	20.8	1,031	916	0.89	43.4	59.1	6.07	15.1	154	
Feb. 21, p.m.	351	106	160	100	60	9	18.9	1,240	1,053	0.85	41.1	61.7	8.43	12.5	119	
Feb. 26, p.m.	234	98	138	98	40	7	15.8	985	819	0.83	33.0	55.7	7.22	11.3	116	
Feb. 28, p.m.	351	107	155	95	60	6	16.9	1,230	1,042	0.85	42.9	63.1	8.08	12.9	120	

F. M., a man, aged 25; height, 178 cm.; weight, 72 Kg.; vital capacity, 5,200 cc.+; diagnosis, mitral insufficiency and stenosis														
Average basal	79	125	86	39	15	6.4	274	220	0.80	39.4	48.4	3.84	5.7	72
Feb. 20, a.m.	234	115	89	41	21	19.4	889	810	0.91	39.7	58.3	7.52	10.8	93
Feb. 20, p.m.	351	121	133	82	56	24.5	1,245	1,138	0.91	43.5	63.3	7.72	14.8	122
I. C., a boy, aged 17; height, 171 cm.; weight, 70.5 Kg.; vital capacity, 3,300 cc.; diagnosis, mitral insufficiency and stenosis and aortic insufficiency (advanced)														
Average basal	67	140	30/0	110	13	5.6	269	208	0.77	39.6	52.1	5.23	4.0	59
Feb. 9, p.m.	234	119	185	60/0	24	20.0	863	814	0.94	41.3	58.7	7.27	11.2	94
S. T., a boy, aged 16; height, 168 cm.; weight, 61 Kg.; vital capacity, 3,400 cc.; diagnosis, mitral insufficiency and stenosis and aortic insufficiency (mild)														
Average basal	80	117	65	52	14	6.0	250	192	0.77	36.5	45.6	3.98	4.8	61
Feb. 16, a.m.	234	104	120	80	40	17.7	607	705	1.16	39.6	62.6	9.00	7.8	76
Feb. 16, p.m.	351	122	140	85	55	23.3	1,013	978	0.97	40.3	63.6	9.12	10.9	89
P. R., a man, aged 42; height, 176 cm.; weight, 69 Kg.; vital capacity, 4,500 cc.; diagnosis, "chronic myocarditis" (?)														
Average basal	75	117	85	32	15	6.3	223	189	0.85	38.4	50.0	5.05	3.8	50
Feb. 15, p.m.	234	117	138	97	41	20.4	714	745	1.04	43.5	62.3	7.82	10.2	87
Feb. 19, p.m.	351	135	145	83	57	23.9	1,050	957	0.91	43.5	63.5	7.77	12.3	91
G. P., a woman, aged 22; height 159 cm.; weight, 55 Kg.; vital capacity, 3,200 cc.; diagnosis, subacute rheumatic fever														
Average basal	76	120	70	50	12	5.2	223	174	0.78	37.2	43.6	2.80	6.2	82
Feb. 11, p.m.	234	126	170	95	75	19.7	839	739	0.88	37.5	55.3	7.31	10.1	80
Feb. 22, p.m.	351	152	145	70	75	27.5	1,053	983	0.93	37.8	57.4	8.03	12.3	81
Feb. 26, p.m.	351	148	165	80	85	24.4	1,030	937	0.91	38.9	59.0	8.27	11.3	77
Feb. 28, a.m.	234	109	140	70	70	18.6	808	688	0.85	33.0	55.6	6.89	10.0	99
M. W., a woman, aged 24; height, 153 cm.; weight, 63 Kg.; vital capacity, 3,500; diagnosis, complete heart block														
Average basal	43	155	65	90	18	6.1	233	182	0.79	40.3	48.3	3.4	5.4	125
Feb. 2, p.m.	234	72	180	85	95	26.0	877	915	1.04	39.4	58.4	7.72	11.8	164
Feb. 19, p.m.	351	87	195	90	105	28.7	1,160	1,076	0.93	41.9	63.1	8.28	13.1	149
J. A., a man, aged 22; height, 178 cm.; weight, 67 Kg.; vital capacity, 4,200 cc.; diagnosis, complete heart block														
Average basal	32	115	55	60	11	4.8	238	184	0.78	39.7	48.8	3.81	4.8	154
Feb. 13, p.m.	234	37	150	50	100	18.0	719	736	1.02	40.9	62.7	8.95	8.2	220
Feb. 18, p.m.	351	38	175	63	107	21.6	857	993	1.16	43.7	69.2	10.0	9.9	258
Feb. 27, p.m.	351	38	165	60	105	21.6	1,051	1,000	0.95	42.4	67.7	9.96	10.1	264

Moderate fatigue of abdominal muscles
Marked fatigue and moderate dyspnea
Performed experiment easier than above

ten minutes apart gave very constant values for oxygen consumption and carbon dioxide production, minute ventilation, and percentage of oxygen and carbon dioxide in the expired air.

Table 2 gives the average minute ventilation, oxygen consumption, carbon dioxide production and respiratory quotient as obtained from two metabolism periods. The alveolar and venous carbon dioxide tensions are averages of four sets of samples or sometimes three when one is obviously incorrect. The pulse, blood pressure and respiration rates represent averages reached during the steady state. The average of two observations under basal conditions (see paper I) is recorded for the patients with heart disease. Case histories of the patients used in this investigation are given in paper I. The two standard grades of work will be referred to in the results as grade 1 and grade 2 work and will denote 234 kilogram meters and 351 kilogram meters per minute, respectively.

RESULTS

Normal Conditions.—Four normal young men, one of whom was obese, were subjected to the same work that was performed by the patients with heart disease. M. F., aged 29, competed in athletic sports only to the extent of playing tennis during the summer. S. L., aged 38, had not taken any regular exercise in recent years but had competed in some minor sports while in high school. E. H., aged 27, competed in athletic sports and had ridden a bicycle frequently while in high school, but had done very little since that time. The results in these normal persons (see table 1) are not very different from those reported by other observers. After grade 2 work, none of the subjects complained of dyspnea, but M. F. and S. L. complained of some fatigue of the legs. The cardiac output with the heavier work varied in these three persons from 12.6 to 14.8 liters a minute. At the same time, the stroke volume varied between 89 and 121 cc. S. L., who had not had routine exercise for many years, had a higher pulse rate and a lower stroke volume during exercise than the other normal subjects.

R. K., aged 29, a fourth normal subject, differed from the others in that he weighed 215 pounds, or 97.5 Kg. (50 pounds, or 22.7 Kg., overweight), and that he had been very active in track, hockey and football while in college, seven years before these observations were made. Five periods of exercise were performed by this subject. He did not complain of fatigue or dyspnea at any time during exercise, but he did volunteer the information that it required much more effort to perform the first two periods of exercise than the subsequent ones, although the fifth represented a heavier grade of work than the first. The effect of repeated exercise (training) is seen in this patient also in the decreasing rate of respiration, pulmonary ventilation per minute and cardiac output and in the increasing arteriovenous differences. The cardiac output decreased from an average of 14.9 liters per minute with an oxygen consumption of 1,250 cc. a minute in the first experiment to

an output of 12.9 liters a minute with an oxygen consumption of 1,230 cc. a minute in the fifth, notwithstanding the fact that a heavier grade of work was used in the latter. These changes were accompanied by an increase in the arteriovenous difference from 6.11 to 8.08 per cent by volume. Since the arteriovenous carbon dioxide difference is an indication of the coefficient of utilization, an increase in oxygen transport occurred. The respiratory rate decreased gradually from 19 in the first experiment to 6 in the fifth, while the ventilation per minute decreased from 22.4 to 16.9 liters a minute. When the respiratory rate was 6 a minute, the tidal air was 66 per cent of the vital capacity. The low respiratory rates are attributed to the patient's former habit of taking as few breaths as possible when competing in short distance runs. The average respiratory quotient of 0.85 is lower than in any of the other exercising subjects and might be explained on the basis of obesity. It seems unlikely that these changes are merely manifestations of a greater familiarity with the procedures, since they came on gradually after several working periods were performed. The other normal subjects showed somewhat comparable effects after repeated periods of exercise but to a lesser extent, as fewer observations were made. The changes noted in these persons probably represent the effects of training. Bock and his associates⁵ have previously pointed out the effects of training in the normal person.

Chronic Rheumatic Valvular Disease.—CASE 1.—Mitral insufficiency and stenosis.

F. M., a man, aged 25, had a mild attack of cardiac decompensation with auricular fibrillation in November, 1928, three and one-half months before these studies were begun. Normal rhythm was restored with the use of quinidine sulphate. At the time of these observations, he had no symptoms of cardiac insufficiency; the pulse rate was slow, and there was no enlargement of the heart.

No dyspnea or fatigue occurred when he performed either the light or the heavy grade of work. On grade 2 work, the cardiac output reached 14.8 liters a minute with an oxygen consumption of 1,245 cc. a minute. The stroke volume was 122 cc., and the arteriovenous carbon dioxide difference 7.72 per cent by volume. These results as well as the respiratory reactions were entirely comparable to those of the normal controls. The pulse pressure, however, averaged about 20 mm. of mercury lower than in the control subjects. This was brought about by the small rise in systolic pressure.

CASE 2.—Mitral insufficiency and stenosis and aortic insufficiency (mild).

S. T., a youth, aged 16, was known to have had valvular disease for four years previous to these investigations but had never had symptoms of cardiac insufficiency. Examination at the time of these observations showed a normal sized heart with a regular rhythm. The patient was considered to be in good physical training as he played basketball three days a week without unusual fatigue or dyspnea.

He carried out both grades of work with less effort than any other patient, including the normal subjects. On grade 2 work the cardiac output increased to 10.9 liters a minute and 89 cc. a beat, with an oxygen consumption of 1,013 cc. a minute. The arteriovenous carbon dioxide difference of 9.12 per cent by volume

was the highest observed in any case of sino-auricular rhythm. The respiration, minute ventilation and pulse rate were similar to those in the normal controls. The pulse pressure was low, being similar in this respect to that in the preceding patient with mitral stenosis. The type of response seen in this patient probably represents a minimum amount of work to the heart and may be ascribed to the patient's trained condition.

CASE 3.—*Mitral insufficiency and stenosis and aortic insufficiency (advanced).*

I. C., a youth, aged 17, had been in the Peter Bent Brigham Hospital with acute rheumatic fever and pancarditis three and a half years before these studies were made, at which time 400 cc. of fluid was removed from the pericardial cavity. At the time of the present observations he complained of dyspnea on moderate exertion. The pulse was regular, and the heart was markedly enlarged, but there were no signs of congestive failure.

With grade 1 work, he experienced moderate dyspnea and marked general fatigue toward the end of the period. After about fifteen minutes, however, he seemed somewhat recovered, but was forced to remain in bed three days with dyspnea and fatigue. During this time he had several small hemoptyses, and for this reason another period of exercise was not attempted. During work, the cardiac output increased to 11.2 liters a minute with an oxygen consumption of 868 cc. a minute, in spite of the patient's advanced heart disease. The stroke volume of 94 cc. and the arteriovenous carbon dioxide difference of 7.27 per cent by volume were within normal limits. The respirations and the minute ventilation were also normal, although increased figures had been expected because of the dyspnea and fatigue. The pulse rate increased from 78 to 119, and the blood pressure rose from 150 mm. systolic and 40 mm. diastolic to 185 mm. systolic and 60 mm. diastolic. Sounds over the brachial artery could be heard down to a zero pressure, but a change in quality occurred at the diastolic pressures indicated. The general reactions found in this patient were not very different from those in normal subjects but the work was performed with much more effort.

CASE 4.—*Subacute rheumatic fever.*

G. P., a woman, aged 23, when first seen in the fall of 1928, five months before these investigations, complained of palpitation, precordial pain and general fatigue. She had an afternoon fever around 99.6 F. which continued through the winter. The blood pressure fluctuated considerably from time to time. In the spring of 1929, she had an initial attack of acutely inflamed joints typical of rheumatic fever. These studies were carried out two months prior to the onset of the joint symptoms. At this time, examination of the heart showed hyperactive sounds and a slight systolic murmur at the apex.

Four observations were made, the first and last with grade 1 work and the second and third with grade 2 work. Dyspnea and palpitation occurred with the heavier work but were not present with the lighter. The patient never complained of very much general fatigue. The cardiac output increased to an average of 10 liters a minute with an oxygen consumption of about 800 cc. a minute with grade 1 work, while with grade 2 work it averaged 11.8 liters a minute with an oxygen consumption of about 1,000 cc. a minute. The stroke volume did not increase above the basal figure of 82 cc. in the first three observations. This unaltered stroke volume was accompanied by an average pulse rate of 150 during grade 2 work. In observation 4, with a grade of work similar to that in the first period there was an increase in the stroke volume to 99 cc. and a slower pulse rate of 109 a minute. The effect of training is suggested by these more normal reactions and by the greater ease with which the latter work was accomplished. The respiration reached 31 a minute and the minute ventilation 27.5 liters in period 2, but such a rise was not observed during other periods of exercise.

TABLE 3.—*The Response of the Pulse and Blood Pressure to Exercise in Patients with Subacute Rheumatic Fever and Complete Heart Block*

Case 4. Subacute Rheumatic Fever									
Feb. 22, 351 kilogram-meters Oxygen consumption, 1,053 cc. per minute Cardiac output, 12.3 liters per minute Stroke volume, 81 cc. per beat					Feb. 26, 351 kilogram-meters Oxygen consumption, 1,030 cc. per minute Cardiac output, 11.3 liters per minute Stroke volume, 77 cc. per beat				
	Pulse Rate	Blood Pressure		Pulse Pressure		Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic				Systolic	Diastolic	
Rest	80	108	68	40	Rest	76	135	88	47
Exercise					Exercise				
1 min.	132	130	68	62	2 min.	136	144	74	70
3	132	140	70	70	5	140	163	78	90
5	140	144	70	74	7	142	163	80	88
7	146	145	70	75	10	142			
8	144	145	70	75	14	144	165	80	85
10	148	144	68	76	15	148	164	78	86
12	...	148	68	80	17	148	164	75	89
15	154	145	68	77	22	156	165	70	95
18	152	144	68	76	23.5	Exercise stopped			
22	152	148	70	78	24	156	162	74	88
24	Exercise stopped				26	122	158	80	78
25	137	132	75	57	27	110	139	84	54
26	108	115	70	45	29	106	136	90	46
28	104	105	74	31	33	96	136	88	48
31	104	104	70	34	35	104	134	88	46
34	90	100	68	32	38	96			
35	90	104	78	26					
38	90								
Case 6. Complete Heart Block									
Feb. 2, 234 kilogram-meters* Oxygen consumption, 877 cc. per minute Cardiac output, 11.8 liters per minute Stroke volume, 164 cc. per beat					Feb. 19, 351 kilogram-meters† Oxygen consumption, 1,160 cc. per minute Cardiac output, 13.1 liters per minute Stroke volume, 149 cc. per beat				
	Pulse Rate	Blood Pressure		Pulse Pressure		Pulse Rate	Blood Pressure		Pulse Pressure
		Systolic	Diastolic				Systolic	Diastolic	
Rest	58	160	75	85	Rest	46	144	70	74
Exercise					Exercise				
3 min.	68	180	85	95	1 min.	68	180	80	100
5	70	180	85	95	8	82			
7	72	185	85	100	10	92	190	90	100
12	78	180	85	95	16	88	190	90	100
16	75	185	85	100	19	82			
21	70	178	78	100	21	..	200	95	105
25	72	180	80	100	27	Exercise stopped			
26	Exercise stopped				28	60	140	60	80
28	60	150	78	72	29	..	140	64	76
30	57	148	75	73	33	52	140	70	70
					36	52	140	68	72
Case 7. Complete Heart Block									
Feb. 13, 234 kilogram-meters Oxygen consumption, 719 cc. per minute Cardiac output, 8.2 liters per minute Stroke volume, 220 cc. per beat					Feb. 18, 351 kilogram-meters Oxygen consumption, 857 cc. per minute Cardiac output, 9.9 liters per minute Stroke volume, 258 cc. per beat				
	Pulse Rate	Blood Pressure		Pulse Pressure		Pulse Rate	Blood Pressure		Pulse Pressure
		Sys-tolic	Dias-tolic				Sys-tolic	Dias-tolic	
Rest	42	115	58	57	Rest	38	120	65	55
Exercise					Exercise				
2 min.	38	145	60	85	2 min.	36	140	68	72
4	38	145	70	75	4	36	155	68	87
6	38	150	60	90	9	38	180	70	110
9	36	150	50	100	12	38	180	63	112
14	37	144	52	92	14	38	180	65	115
17	37	150	50	100	18 (aur. 126)‡				
21	..	146	50	96	21 (aur. 126)	160	65	95	
22	Exercise stopped				22	40			
23	41	140	50	90	24	Exercise stopped			
25	43	130	70	60	24.5 (aur. 134)	155	60	95	
26	43	120	70	50	25	42			
27	..	115	60	55	27	42	140	70	70
28	42	120	70	50	29	40	125	70	55
					32	40	120	70	50
Feb. 27, 351 kilogram-meters Oxygen consumption, 1,051 cc. per minute Cardiac output, 10.1 liters per minute Stroke volume, 264 cc. per beat									
	Pulse Rate	Blood Pressure		Pulse Pressure		Pulse Rate	Blood Pressure		Pulse Pressure
		Sys-tolic	Dias-tolic				Sys-tolic	Dias-tolic	
Rest	36	115	70	45	Rest				
Exercise					Exercise				
3 min.	34	145	55	90	3 min.	34	145	55	90
5	34	150	52	98	5	34	150	52	98
8	36				8	36			
9 (aur. 134)		170	60	110	9 (aur. 134)		170	60	110
14	38	165	65	100	14	38	165	65	100
16	37	170	58	112	16	37	170	58	112
18 (aur. 130)					18 (aur. 130)				
19	38	165	55	110	19	38	165	55	110
22	Exercise stopped				22	Exercise stopped			
23	..	140	60	80	23	..	140	60	80
27	44	130	70	60	27	44	130	70	60
30	40	115	70	45	30	40	115	70	45

* About five extrasystoles per minute during exercise.

† Very numerous extrasystoles during exercise.

‡ Auricular rate counted by venous pulsations.

An interesting manifestation of the instability of the vasomotor system is seen in the second and third observations performed four days apart under very similar conditions (table 3). The circulatory response was almost the same except for the blood pressures. In the second observation, the resting blood pressure of 108 mm. systolic and 68 mm. diastolic rose to 148 mm. systolic and 70 mm. diastolic; in the third observation, the resting blood pressure of 135 mm. systolic and 88 mm. diastolic rose to 168 mm. systolic and 80 mm. diastolic. Thus it can be seen that the resting systolic pressure was 27 mm. higher in the latter working period. In both experiments, the blood pressure dropped back almost to its exact resting level after exercise was stopped. In each instance, the pulse rate failed to reach its former resting level after a fifteen minute rest period on the bicycle.

CASE 5.—*"Chronic myocarditis" (?)*.

P. R., a man, aged 43, was admitted to the Peter Bent Brigham Hospital in December, 1928, two months previous to these studies, with a history of dyspnea on exertion of several months' duration. Examination revealed auricular fibrillation, a normal sized heart, and a positive blood Wassermann reaction. Normal rhythm was restored by the use of quinidine sulphate. At the time of these observations, two months after discharge from the hospital, there were no symptoms or signs of cardiac insufficiency, and the rhythm was regular.

The muscular work caused some fatigue of the legs but no dyspnea. The cardiac output reached 12.3 liters a minute with an oxygen consumption of 1,050 cc. a minute. The stroke volume, arteriovenous carbon dioxide difference, respiration, minute ventilation and pulse rate reacted as in the normal subjects. The pulse pressure of 57 mm. of mercury during grade 2 work was lower than in the normal subjects and in this respect the patient was similar to the two patients with mitral stenosis (cases 1 and 2).

CASE 6.—*Complete heart block.*

M. W., a woman, aged 24, visited the outpatient department in January, 1929, one month before these studies were begun. The only complaint was backache. There was a history of diphtheria with complete heart block as a complication at the age of 5. Physical examination revealed a pulse rate of 48 and a slightly enlarged heart. An electrocardiogram showed complete auriculoventricular block.

Observations were made, the two standard grades of work being used. Moderate dyspnea and marked fatigue occurred, especially with grade 2 work. With this work, it seemed doubtful whether the patient would be able to finish the period of exercise, and afterward she stated that it was the maximum of which she was capable. No cyanosis or distention of the jugular veins was observed while she was exercising. The cardiac output increased to 13.1 liters a minute with an oxygen consumption of 1,160 cc. a minute on grade 2 work. The stroke volume increased from 125 cc. in the basal state to 149 cc. during the heavier work. With the lighter work, there were fewer extrasystoles than with the heavier, and the stroke volume was 164 cc. During exercise, the arteriovenous carbon dioxide difference did not exceed normal values. The respiratory rate of 33 and the minute ventilation of 28.7 liters were comparable to those in patient 4, who had a rheumatic infection. The heart rate (table 3) with the first grade of work rose from 58 to an average of 72 a minute, and the rise was accompanied by about six extrasystoles a minute. On grade 2 work, the heart rate rose from 46 to an average of 87 beats a minute. This was accompanied by numerous extrasystoles which made the heart seem totally irregular; its rate could be determined only by direct auscultation. An electrocardiogram, taken at another time directly following mild exercise, showed an increase in the ventricular rate from 40 to 50, while the auricle increased its rate from 90 to 120. The auricular and ventricular rhythms were completely

dissociated and no extrasystoles occurred. During grade 2 work on the bicycle, the blood pressure increased from 144 mm. systolic and 70 mm. diastolic to 195 mm. systolic and 90 mm. diastolic, resulting in the high pulse pressure of 105 mm. This case illustrates a type of complete heart block in which the ventricular rate is capable of increasing by the same percentage as that of a normal person. This increase was due both to a regular ventricular acceleration and to ventricular extrasystoles, and served in maintaining an adequate blood flow during muscular activity.

CASE 7.—*Complete heart block.*

J. A., a man, aged 22, was found to have complete heart block in July, 1927, seven weeks after an infection of the foot. A year and a half later, when these studies were made, he was able to be moderately active without symptoms. The heart was slightly enlarged and the rate was 36 a minute. An electrocardiogram showed complete auriculoventricular block.

With the lighter grade of work there was no dyspnea, but he complained of moderate general fatigue and epigastric discomfort. In two observations with the heavier work, the patients experienced moderate dyspnea and quite marked fatigue, the effects of which persisted for several days. No cyanosis was noted during the exercise. The cardiac output was 8.2 liters a minute with an oxygen consumption of 719 cc. a minute on grade 1 work. With the heavier grade of work, it reached 10.1 liters a minute with an oxygen consumption of 1,051 cc. a minute. This was the lowest output observed in any subject in the series on grade 2 work, and was probably due to the inability of the ventricle to increase its rate. The stroke volume reached the very high level of 264 cc., which is a reflection of the failure of the ventricular rate to increase. Liljestrand and Zander⁸ stated that the highest stroke volume reported in the literature is 208 cc., which was observed by Lindhard¹³ in an athlete when the oxygen consumption was 3,204 cc. a minute. In our case, the arteriovenous carbon dioxide difference reached 10 per cent by volume, the highest figure in this series. This was brought about by a rise in the venous carbon dioxide tension to 69.2 mm. of mercury. The respiratory rate and the minute ventilation were within normal limits. The heart rate, during the resting period on the bicycle, ranged from 36 to 42 a minute (table 3). Immediately after exercise was begun, the heart rate decreased from 2 to 4 beats a minute. After about ten minutes of exercise it returned to its resting level. When exercise was stopped, there was an immediate increase in the heart rate of from 4 to 6 beats, after which it gradually fell back toward its resting level. During work, the jugular veins were distended and auricular pulsations, which were plainly visible, averaged about 130 beats a minute. The blood pressure reaction, typically shown in the third observation, was 115 mm. systolic and 70 mm. diastolic in the preliminary rest period, while during exercise it rose to an average of 165 mm. systolic and 60 mm. diastolic. This patient illustrates the type of heart block in which the ventricular rate does not increase under exertion. An increased cardiac output is maintained by the high stroke volume, and the oxygen supply to the tissue is aided by the increased coefficient of utilization.

COMMENT

It can be seen in table 4 that the cardiac output in all subjects varied between 10.1 and 14.8 liters a minute while they were performing a

13. Lindhard, J.: Ueber das Minutenvolum des Herzens bei Ruhe und bei Muskelarbeit, Arch. f. d. ges. Physiol. **161**:233, 1915.

grade of work of 351 kilogram meters a minute on the stationary bicycle ergometer. There were no very significant differences in the cardiac output between the normal subjects and the patients with heart disease. The lowest values occurred in patient 2, a youth in good physical training with mild valvular disease, and in patient 7, who had complete heart block. Patient 2 performed the work with great ease, while patient 3 experienced considerable distress and fatigue. In both subjects, the increased oxygen consumption was associated with an unusual increase in the arteriovenous carbon dioxide difference, which indicates a greater oxygen exchange between the blood and the tissues. It appears that the trained person (patient 2) performed the work in a very economical fashion. The difficulty that patient 7 experienced in performing the work might be attributed to the changes in cardiac function that accompany the 100 per cent increase in the output of the heart without an increase in the ventricular rate.

TABLE 4.—*Cardiac Output, Pulse Rate, Stroke Volume and Pulse Pressure of Normal Subjects and of Patients with Heart Disease While Performing Work Amounting to 351 Kilogram Meters a Minute**

Subject	Cardiac Output, Liters per Minute	Heart Rate per Minute	Stroke Volume, Cc.	Pulse Pressure, Mm. Hg.
M. F. Normal	14.8	122	121	75
S. L. Normal	13.6	130	105	70
E. H. Normal	14.4	120	120	77
R. K. Obese normal	12.9	107	120	60
F. M. Mitral stenosis	14.8	121	122	56
S. T. Mitral stenosis; aortic insufficiency	10.9	122	89	55
P. R. Chronic myocarditis	12.3	135	91	57
G. P. Subacute rheumatic fever.....	12.3	152	81	75
M. W. Heart block	13.1	87	149	105
J. A. Heart block	10.1	38	264	105

* Patient 3 is omitted, as the grade of work was too strenuous for him.

With an increase in cardiac output such as was seen in these cases, a slow pulse rate was associated with a high stroke volume, and vice versa, as would be expected. This phenomenon is illustrated in its most marked form in patient 7, who had complete heart block, and in patient 4, who had subacute rheumatic fever. Patient 7 could not increase his pulse rate above 38 beats a minute, and since the cardiac output was 10.1 liters a minute, the stroke volume was thereby increased to 264 cc. Patient 4 had a heart rate of 150 a minute during exercise. This resulted in an average stroke volume of 79 cc. (two observations), which was slightly below the resting level. Both patients performed the work with some dyspnea and fatigue. In the normal subjects or in those with more normal responses, the pulse rate and stroke volume both approached a figure of 120 for the heavier grade of work. No general correlation apparently existed between the blood pressure and the stroke volume. In the patients with heart block, however, the pulse pressure showed an appreciable increase along with the high stroke volume.

Peabody and Sturgis¹⁴ found an increased oxygen consumption and pulmonary minute ventilation in patients with heart failure when at rest. No significant difference in the oxygen consumption and minute ventilation was observed between our patients, who had compensated heart disease, and the normal subjects. The two women, however (patients 4 and 6), had higher respiratory minute volumes than the men, with approximately the same oxygen consumptions. We cannot assume that these higher values were related to the cardiac condition, as no observations were made in women with normal hearts.

The respiratory quotients were for the most part between 0.90 and 1. In two instances (patients 7 and 2), we observed average values of 1.16, which were approximately the same at the beginning and at the end of the periods of exercise. In repeated observations, the respiratory quotients for these two patients were 0.95 and 0.97, respectively. The explanation of this discrepancy is not clear.

Vital capacities were taken at rest and again just before exercise was stopped. Little difference was noted in the two records. Patients who experienced some dyspnea during exercise showed the following average variations in the vital capacities from the resting levels: Patient 3, an increase of 100 cc.; patient 4, a decrease of 100 cc., and patient 6, a decrease of 600 cc.; patient 7 showed no change. Except for patient 6, who had complete heart block, the changes in the vital capacity during rest and exercise were negligible. If any change in the pulmonary blood volume occurred in the patients with mitral stenosis, it was not shown by changes in the vital capacities.

Values for the carbon dioxide tension of the arterial and venous bloods during exercise are shown in table 2. A marked rise occurred in the venous carbon dioxide, while the alveolar carbon dioxide showed only a slight increase or remained unchanged. The arteriovenous difference, then, was increased largely by the rise in the venous carbon dioxide. This observation is of interest when compared with changes in the arteriovenous differences of patients studied at rest. It was shown in paper I that changes in the arteriovenous difference in carbon dioxide accompanying variations in the cardiac output at rest are the result principally of changes in the arterial carbon dioxide level.

When the increased arteriovenous difference of carbon dioxide found during exercise is interpreted in terms of oxygen exchange, it means that there is an increase in the coefficient of oxygen utilization. The increased oxygen demand is met, therefore, by an increase both in the

14. Peabody, F. W., and Sturgis, C. C.: Clinical Studies on the Respiration: IX. The Effect of Exercise on the Metabolism, Heart Rate, and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, *Arch. Int. Med.* 29:277 (March) 1922.

output of the heart and in the coefficient of utilization. We have already suggested that training seems to increase the coefficient of utilization. The circulation, then, may be more economical as a result of training, since it allows the increased oxygen demand during exercise to be met by a greater oxygen utilization, with less blood required by the tissues.

In our studies we have shown that the cardiac output responded to a standard grade of work in a similar manner in normal persons and in those with compensated heart disease. This is consistent with the work of some authors who have found that the output of the heart is a function of the respiratory metabolism. If the heart could not have maintained an adequate circulation with the grade of work used, a cumulating oxygen debt would have ensued and exercise could not have been continued for a long period. Although the response of the cardiac output was quite similar in all of the subjects studied, several of the patients with heart disease experienced dyspnea, fatigue and general distress, symptoms that were almost negligible in the normal subject. These adverse subjective reactions were not related to any considerable variation in the measurable cardiac output.

It is a striking fact that the subjective symptoms accompanying work in patients with cardiac disease are very evident when the several measurable factors of these observations change essentially as they do in those with normal hearts under the same conditions of work. There are yet some unknown factors present in the circulatory mechanism of patients with heart disease. These are manifested by symptoms of dyspnea and fatigue on exertion but are, at the present time, unmeasurable by determinations of the cardiac output, stroke volume, vital capacity or respiratory minute ventilation.

SUMMARY

1. Four normal subjects and seven patients with compensated heart disease, including chronic rheumatic valvular disease, subacute rheumatic fever, "chronic myocarditis" (?) and complete heart block, were subjected to two moderate, standardized grades of work on the Krogh bicycle ergometer. Measurements were made of the cardiac output, pulse rate and blood pressure during exercise.

2. The response of the cardiac output in the patients with heart disease was not essentially different from the response in the normal subjects. The lowest values occurred in a youth in good physical training with mild valvular disease who performed the work with ease, and in a young adult with complete heart block who performed the work with difficulty.

3. Four of the patients with heart disease experienced fatigue and dyspnea during exercise. Fatigue was usually more marked than dyspnea.

The first patient had advanced aortic and mitral disease with marked cardiac enlargement. The pulse pressure, which was abnormally high at rest, increased relatively as in the normal subjects during exercise. The second patient, who had subacute rheumatic fever, had an abnormal increase in the pulse rate, while the stroke volume did not rise above its basal level. In the third, a young woman with complete heart block, the pulse rate doubled during exercise. This was effected both by an increase in the ventricular rate and by the occurrence of extrasystoles. The fourth patient, a young man with complete heart block, had a slight decrease in the pulse rate during exercise. This was accompanied by a greatly increased stroke volume, higher than any previously reported in the literature. Both patients with complete heart block had an unusual rise in the pulse pressure during work.

4. The effect of training is indicated by the more efficient response seen in a patient with mild valvular disease who had been accustomed to strenuous exercise, and in several of the other subjects after they had performed repeated periods of work on the bicycle.

THE SIGNIFICANCE OF AXIS DEVIATION IN THE HUMAN ELECTROCARDIOGRAM

A COMPARISON OF ELECTRICAL AXIS WITH ROENTGEN RAY
AND CLINICAL OBSERVATIONS IN THREE HUNDRED
AND THIRTY-FOUR CASES *

SAMUEL H. PROGER, M.D.

ATLANTA, GA.

AND

DAVID DAVIS, M.D.

BOSTON

For purposes of understanding the significance of electrical axis or axis deviation, the heart may be regarded as a strip of muscle. If the two electrodes of a galvanometer make contact at *A* and *B* of a muscle strip (fig. 1), and the current runs parallel to and in the plane of the electrodes, a deflection occurs. If the electrodes are at *X* and *Y*, the electrical fields at these points approach a balance, little or no difference of potential is present, and practically no deflection occurs. For purposes of simplification, contacts *A-B* may be likened to lead I, and points *X-Y* to lead III. If three leads are so arranged as to form an equilateral triangle, an idea of the position of the muscle strip may be obtained by comparing the height of the deflections in the three leads. In figure 2 *A*, it is noted that lead II lies in the direction of the muscle strip, and is therefore in a position to record maximum voltage and greatest deflection. When the muscle strip lies horizontal, as in figure 2 *B*, lead I will record the greatest difference of potential; in the position shown in figure 2 *C*, the maximal excursion will be indicated in lead III. In a similar manner, by noting the respective heights of the R waves in the human electrocardiogram, one can obtain an idea of the general position of the electrical axis of the heart.

In well defined left axis deviation, the R wave is relatively high in lead I; the S wave, deep in lead III. In right axis deviation, the relation is reversed, the R wave being high in lead III and the S wave deep in lead I. These variants may be employed to portray in a general way the electrical axis of the heart. Two general methods for determining this axis have come into use. One expresses the axis in terms of degrees of an angle; the other, as an index.

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* From the Medical Clinic of the Boston Dispensary, service of Dr. Joseph H. Pratt.

The first method of determining electrical axis was introduced by Einthoven,¹ who expressed this axis as an angle (angle alpha) which is arbitrarily measured from a horizontal plane, as in figure 3 (modified from Einthoven). This angle is determined by a consideration of the height of a certain deflection at a given time simultaneously in the three

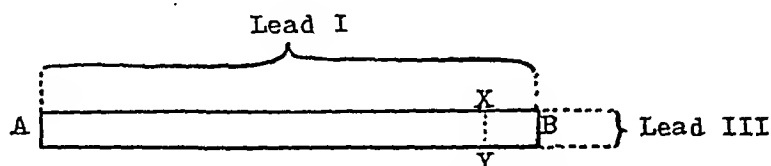


Fig. 1.—Diagrammatic sketch of heart illustrating deflection caused by the contact of two electrodes at *A* and *B*, with the current parallel to, and in the plane of the electrodes. If the electrodes are at *X* and *Y*, little or no deflection occurs.

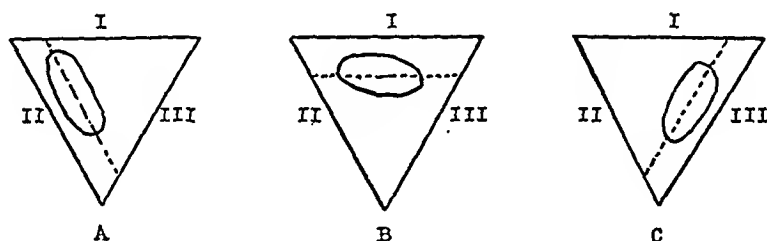


Fig. 2.—Illustration of the deflection due to the position of the muscle strip. In figure 2 *A*, lead II lies in the direction of the muscle strip and records maximum deflection. In figure 2 *B*, the muscle strip lies in a horizontal position and lead I records the greatest difference in potential. In figure 2 *C*, the maximal excursion is indicated in lead III.

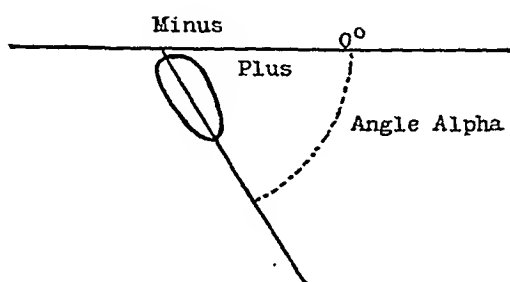


Fig. 3.—Diagrammatic illustration of the first method of determining electrical axis, by expressing this axis as angle alpha.

leads. He has shown mathematically that if one regards the three leads as the sides of an equilateral triangle, the value of any point of the QRS complex in lead II will be equal to the sum of the values of the

1. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen in Menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275 (March) 1913.

simultaneous points in leads I and III.² When the peaks of only two waves are approximately in phase, the value in the third lead may be obtained by the formula: lead II = lead I + lead III. In right predominance, the peaks of the R waves in leads II and III are usually found to be practically in phase, whereas in left predominance the peaks of the R waves in leads I and II generally occur almost simultaneously. The values of the R peaks may then be taken as the values e_1 , e_2 and e_3 of Einthoven's formulas and the electrical axis determined as an angle accordingly. Or, the value of the highest peak may be reduced to a scale of 10, the others reduced correspondingly, and, using Einthoven's tables,³ the degree of the angle determined. Einthoven considered an angle between 40 and 90 degrees as normal, below 40 degrees as constituting left deviation and above 90 degrees as right deviation. Waller⁴ has suggested —10 degrees to 100 degrees as normal limits. A modification of Einthoven's method has been presented by Carter,⁵ who takes 0 to 90 degrees as normal limits, as does Dieuaide.⁶

The other general method of determining axis deviation is by means of an index, as suggested by Lewis.⁷ Lewis' formula is as follows: $(R_1 + S_3) - (S_1 + R_3) = \text{Index}$. R and S are expressed as the heights in tenths of a millivolt of these waves in the respective leads indicated by the numerals. A value above +20 is considered left axis deviation; below —15, right deviation. White's formula, $(U_1 + D_3) - (D_1 + U_3)$ is similar, U corresponding to the upward deflection and D to the largest of the downward deflections, whether it be Q, R or S. Pardee⁸ has critically compared these methods of Einthoven, Carter, Lewis and White.

There are differences of opinion concerning the value of the electrical axis as an index of relative hypertrophy of the ventricles. Present knowledge is based on the following correlations: (1) a comparison of the axis deviation with the relative weights of the heart chambers

2. Einthoven, W.: Weiteres über das Elektrokardiogram, *Arch. f. d. ges. Physiol.* **122**:558, 1908.

3. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, New York, Paul B. Hoeber, Inc., 1925, p. 204. Einthoven (footnote 1).

4. Waller, A. D.: *Proc. Roy. Soc., London* **88B**:49 (Aug.) 1914.

5. Carter, E. P.; Richter, C. P., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* **30**:162 (June) 1919.

6. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, *Arch. Int. Med.* **27**:558 (May) 1921.

7. Lewis, T.: Observations on Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber, *Heart* **5**:367, 1913.

8. Pardee, H. E. B.: Determination of Ventricular Preponderance from the Electrocardiograph, *Arch. Int. Med.* **25**:638 (June) 1920.

determined post mortem; (2) a comparison of the axis with clinical observations—for example, hypertensive heart disease usually gives rise to relatively greater hypertrophy of the left ventricle, while pulmonary and mitral stenosis generally produce relative hypertrophy of the right ventricle; (3) a comparison of the axis with an orthodiagram of the heart.

The first method is obviously the most exact. Thus far, however, the total number of such correlations has not exceeded 74 (Lewis,⁷ Cotton,⁹ Herrmann¹⁰). A comparison with clinical observations should be of value if the number of cases is large, and the clinical diagnoses are well founded. Such a study has been made by Bridgman,¹¹ White and Bock¹² and White and Burwell.¹³ A comparison of electrical axis with orthodiagrams alone is the least satisfactory method for the reason that hypertrophy of one or the other chamber is not necessarily made evident by the teleoroentgenogram.

Soon after Einthoven¹⁴ pointed out the relation of deviation to preponderance, many considered this relation almost constant. This idea was further strengthened by the observations of Lewis,⁷ who, by comparing the electrocardiograms with the postmortem weights of each ventricle separately in nine cases, showed that, barring slight deviations, left axis deviation usually meant left-sided preponderance, and that right axis deviation even more constantly meant right-sided hypertrophy or relative preponderance. This work was substantiated by Cotton⁹ in a study of six additional cases. White and Bock,¹² using Lewis' formula for axis deviation, compared clinical diagnoses with electrocardiograms in 104 cases. They found that in 26 cases showing marked deviation to the right or left (over $+30$ and beyond -18) all the right deviations occurred in cases of mitral stenosis, rheumatic heart disease with stenosis, congenital heart disease, or chronic emphysemas, whereas all left deviations occurred in either aortic regurgitations or hypertensive hearts without aortic regurgitation. They found also that in 3 of 7 cases with slight right axis deviations the hearts were normal

9. Cotton, T. F.: Observations on Hypertrophy, *Heart* **6**:217, 1915.

10. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Postmortem Observation, *Heart* **9**:91, 1922.

11. Bridgman, E. W.: The Value of the Electrocardiogram in the Diagnosis of Cardiac Hypertrophy, *Arch. Int. Med.* **15**:487 (March) 1915.

12. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am. J. M. Sc.* **156**:17 (July) 1918.

13. White, P. D., and Burwell, C. S.: The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiograph, *Arch. Int. Med.* **34**:529 (Oct.) 1924.

14. Einthoven, W.: Le télécardiogramme, *Arch. internat. de physiol.* **4**:132, 1906.

while in only 8 of 61 cases of slight left axis deviations was this true. White and Burwell¹³ reviewed 288 cases of right axis deviation and 398 of left axis deviation and obtained similar results. The observations of White and Bock, and White and Burwell then appeared to attach a real clinical significance to axis deviation, and their work indicated that cases of marked deviation bear a fairly constant relation to definite clinical conditions. They compared only the clinical observations with the electrocardiogram and did not consider the size and position of the heart. Carter and Greene¹⁵ concluded from clinical impressions and from the work of Lewis and Cotton that the electrocardiogram is the only satisfactory method of estimating relative preponderance, and that, considered with the teleoroentgenogram, it is a valuable guide to gross hypertrophy. Pardee⁸ suggested a relationship between axis deviation and the position of the heart in the chest and believed this relationship would account for certain apparent discrepancies between axis deviation and ventricular preponderance.

The work of Herrmann and Wilson,¹⁰ however, has thrown doubt on the clinical interpretation of axis deviation. Using a technic similar to Lewis' for determining the weights of the ventricles, and studying a larger series of fifty-nine cases, they concluded that relative weight is only one of many factors influencing electrical axis, and that it predominates only when the heart is greatly hypertrophied. They thought the disturbing factors to be (*a*) variations in the position of the heart, (*b*) variations in arrangements of conducting systems and (*c*) disturbances of atrioventricular conduction. They accounted for the discrepancy between their conclusions and those of Lewis by the fact that all the hearts in Lewis' series were large, and in very large hearts the relative weight is the chief factor influencing axis deviation.

Fahr¹⁶ has maintained that the form of the electrocardiogram in enlargement of one side or the other is due to increased length of the conducting path in one or the other ventricle. If this is true, dilatation must also be considered in the production of axis deviation. Cohn and Raisbeck,¹⁷ also Meek and Wilson,¹⁸ showed experimentally that changes in position may produce appreciable changes in axis. Meek and Wilson emphasized the significance of rotation of the heart on its

15. Carter, E. P., and Greene, C. H.: The Electrocardiogram and Ventricular Preponderance, *Arch. Int. Med.* **24**:638 (Dec.) 1919.

16. Fahr, G.: Analysis of Spread of Excitation Wave, *Arch. Int. Med.* **25**: 146 (Feb.) 1920.

17. Cohn, A. E., and Raisbeck, M. J.: Relation of Position of Enlarged Heart to Electrocardiograph, *Heart* **9**:331 (Dec.) 1922.

18. Meek, W. J., and Wilson, A.: The Effect of Changes in Position of the Heart on the Q R S Complex of the Electrocardiogram, *Arch. Int. Med.* **36**: 614 (Nov.) 1925.

longitudinal axis in influencing this deviation. Reid¹⁹ has recently concluded from a comparison of 100 orthodiagrams with electrocardiograms that the axis is no satisfactory guide to relative ventricular hypertrophy.

It would appear, then, from an analysis of the literature that the problem of the value of axis deviation is still unsettled. In the present study, the electrical axis is compared with both the roentgenologic observations and clinical diagnoses in 334 cases. The electrical axis was determined by finding the angle alpha according to Einthoven¹ (fig. 3). The two largest R waves were generally chosen, but only when their peaks appeared approximately at the same moment in the cardiac cycle. The patients were for the most part ambulatory. The majority of the roentgenograms taken were orthodiagrams and the remainder were plates of the heart taken at a distance of 2 meters. They were taken with the patient in the erect position; the electrocardiograms, in the recumbent position. The cardiac measurements and electrocardiograms were in almost all cases taken within the same week. The records used showed no evidence of disturbance in conduction. The patients regarded as having hypertension showed a minimal systolic pressure of 170 mm. of mercury.

In the following analysis, the degree of deviation is designated normal when it is between 40 and 90 degrees; slight left when 20 to 40 degrees; moderate left, 0 to 20 degrees; marked left, below 0 degree, and right, above 90 degrees. The enlargements of the heart are classified as left, generalized or right. A further classification is made of left enlargements as slight, moderate and marked. Enlargements were all definite; the questionable variations were rejected. Otten's²⁰ orthodiagraphic standards were used.

NORMAL HEARTS

Of the 68 hearts which were normal roentgenographically and clinically, 46 (or 67 per cent) had normal angles; 14 (or 21 per cent) showed slight left deviation; 6 (or 9 per cent) moderate left deviation, and 2 (or 3 per cent) marked left deviation. Thus it is seen that only 12 per cent of the normal hearts had angles below 20 degrees and only 3 per cent below 0 degree. It is interesting to note that no normal heart in this series showed an angle over 80 degrees.

The positions of the heart were classified as vertical, oblique or transverse. Although it is fairly certain that change in position is a

19. Reid, W. D.: Comparison of Electrical Axis Shown by Electrocardiograph with Roentgen Mensuration, *Am. Heart J.* 4:223 (Dec.) 1928.

20. Otten, M.: Die Bedeutung der Orthodiographie für die Erkennung des beginnenden Herzweiterung, *Deutsches Arch. f. klin. Med.* 105:370, 1911.

factor in determining electrical axis, nevertheless varying positions as ordinarily observed in the roentgenogram were found not to be paralleled with any degree of regularity by changes in axis. For example, several normal hearts with definitely vertical positions showed angles below 70 degrees. Also, no constant relationship was noted between the electrical axis and the transverse position of the heart.

PATHOLOGIC HEARTS OF NORMAL SIZE

Twenty-seven hearts of normal size were classed as definitely pathologic on clinical examination. Twelve of these were cases of hypertensive heart disease, three showing normal angles, three slight left deviations and six moderate left deviations. Eleven were cases of arteriosclerotic heart disease. One of these had a normal angle, 2 showed slight left deviation, 4 moderate left deviation, and 3 marked left deviation. There

TABLE 1.—*Enlarged Hearts*

	Marked Left	Moderate Left	Slight Left	Nor- mal	Slight Right 80-90	Right
Rheumatic mitral stenosis.....	2	2	3	14	7	9
Hypertensive heart disease.....	23	32	21	7
Syphilitic aortic regurgitation.....	2	1
Congenital pulmonic stenosis.....	1	..	5
Chronic emphysema	1
Others	10	17	16	33	1	..
Totals.....	37	51	40	56	8	15

were 4 cases of mitral stenosis, and all showed normal angles. The angle in one of the latter was 88 degrees. Thus, only 8 of 27 pathologic hearts of normal size presented normal angles.

ENLARGED HEARTS

There were 207 definitely enlarged hearts with the following clinical diagnoses: essential hypertension, 83; rheumatic heart disease, 37; syphilitic aortic regurgitation, 3; congenital heart disease, 6; chronic emphysema, 1, and miscellaneous, 77 (table 1). Of the 83 patients with hypertension, 76 showed left deviation varying from slight to marked, while only 7 had normal angles. This type of heart disease is, of course, commonly associated with left ventricular preponderance. According to Lewis' ⁷ postmortem studies, relative left ventricular preponderance is found more constantly in hypertensive heart disease than in any other type. Of the 3 syphilitic hearts with aortic regurgitation, 2 showed marked left deviation and 1 a normal axis. There were 37 enlarged hearts with rheumatic mitral stenosis. Of these, 21 were normal, 7 ranging between 80 and 90 degrees. In 9 the angle was above 90 and in 7 below 40 degrees. Of the latter, 4 were associated with aortic insufficiency and 1 with hypertension. Of 6 with congenital heart

disease, 5 showed right axis deviation, and in 1 the angle was normal. All enlarged hearts with right axis deviation presented either mitral stenosis, congenital heart disease or chronic emphysema.

COMPARISON OF ROENTGENOGRAM WITH ELECTRICAL AXIS

In this series, there appear no significant relationships between the orthodiagraphic heart size and electrical axis. For example, of 87 enlarged hearts, the gross roentgen ray appearance of which was much the same, namely, left-sided enlargement, there were 37 with marked left axis deviation and 50 with normal angles. Of the 21 cases of right-sided predominance from the roentgen ray standpoint, 1 showed slight left deviation and 13 normal angles, while only 7 gave definite electrocardiographic signs of right preponderance. Of 103 hearts of normal size, 47 were within the normal limits and 56 showed slight to marked left deviation.

TABLE 2.—*Distribution of Axis According to Size of Heart*

Size	Below 0	0-10	10-20	20-30	30-40	40-50	50-90	Over 90
Normal	7	8	12	6	23	45	2	..
Questionable enlargement	4	1	4	4	3	7
Slight enlargement	19	9	15	12	10	27	2	2
Moderate enlargement	9	13	7	4	6	14	..	3
Marked enlargement	9	3	4	4	3	9	..	3
Primarily right enlargement.....	1	7	6	7

These observations do not indicate that axis deviation is without significance, since the orthodiagram is not a satisfactory indicator of relative ventricular preponderance. As Bardeen²¹ has indicated, only hypertrophy as a whole can be determined by roentgen ray examination. It follows, then, that a comparison of roentgen ray observations alone with electrical axis is of little or no value, and that conclusions based on this correlation are not justified.

PROPOSED CHANGE OF NORMAL LIMITS

In the present series there were 68 normal hearts. Not one of these showed an angle as high as 80 degrees. Of the 10 cases with angles between 80 and 90 degrees, 8 were cases of mitral stenosis and 6 of these appeared definitely enlarged to the right on the orthodiagram. This indicates that 80 degrees might be considered the upper limit of right deviation, rather than 90 degrees as suggested originally by Einthoven. This is in accordance with the views of White and Burwell,¹⁸ who, after observing for many years the significance of axes determined by Lewis' formula, felt that — 10 instead of — 15 degrees

21. Bardeen, C. R.: Determination of the Size of the Heart by Means of X-Rays, *Am. J. Anat.* 23:423 (March) 1918.

should be the borderline of normal with respect to right axis deviation. Such a change in the Lewis formula corresponds to a change in the angle, as suggested herewith. Further, the fact that a number of normal hearts show angles between 0 and 40 degrees warrants the acceptance of zero degree as the limit of left deviation rather than 40 degrees as proposed by Einthoven. The foregoing observations therefore suggest that 0 to 80 degrees be regarded as the limits of normal axis deviation, with the possibility in infrequent cases of limits of -10 and 90 degrees.

SUMMARY AND CONCLUSIONS

1. The present status of the clinical significance of axis deviation in the human electrocardiogram is reviewed. The electrical axes, orthodiagrams and clinical observations are compared in 334 cases.

2. Clinical conditions generally associated with left ventricular preponderance tend to produce left axis deviation; those associated with right ventricular preponderance more constantly produce right deviation. This occurs more regularly in enlarged hearts than in hearts of normal size.

3. Sixty-six of 68 normal hearts on clinical and orthodiagraphic examination presented angles varying from 0 to 80 degrees. Zero to 80 degrees is therefore proposed as the limits of normal with the possibility in infrequent cases of limits of -10 to 90 degrees.

I. THE DIFFUSIBLE CALCIUM AND THE PROTEINS OF THE BLOOD SERUM IN JAUNDICE*

LEWIS GUNTHER, M.D.

LOS ANGELES

AND

D. M. GREENBERG, Ph.D.

WITH THE TECHNICAL ASSISTANCE OF MR. JOHN B. DALTON

BERKELEY, CALIF.

Investigations into the state of the blood calcium in diseases accompanied by jaundice have been carried out mainly in three directions: the direct examination of the total calcium content of the whole blood, serum or plasma of jaundiced patients and experimental animals; the determination of the toxicity of bile and bile salts as modified by the action of calcium salts, and the injection of these into the blood stream of experimental animals; and by therapy with calcium salts, cod liver oil and ultraviolet radiation, and by the action of extract of parathyroid hormone in experimental animals and in man.

The most consistently and most widely quoted works are those of King and Stewart,¹ Lee and Vincent,² Vines,³ Groves and Vines,⁴ Kirk and King,⁵ and Walters and Bowler.⁶ It is largely on the basis of these investigations, in which the three methods of approach mentioned were employed, that the current opinion rests for the existence of a deficiency in available calcium of the blood of jaundiced patients.

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* From the Department of Medicine, San Francisco, and the Division of Biochemistry, Berkeley, University of California Medical School.

* This research is one of a series carried out jointly by the Department of Medicine and the Division of Biochemistry of the University of California Medical School, with the cooperation of Professors W. J. Kerr and Carl L. A. Schmidt.

1. King, J. H., and Stewart, H. A.: Effect of the Injection of Bile on the Circulation, *J. Exper. Med.* **11**:673, 1909.

2. Lee, R. I., and Vincent, B.: The Relation of Calcium to the Delayed Coagulation of the Blood in Jaundice, *Arch. Int. Med.* **16**:59 (July) 1915.

3. Vines, H. W. C.: The Coagulation of the Blood; I. The Rôle of Calcium, *J. Physiol.* **55**:86, 1921.

4. Grove, W. R., and Vines, H. W. C.: Calcium Deficiencies, Their Treatment by Parathyroid Extract, *Brit. M. J.* **1**:791 (May 20) 1922.

5. Kirk, P. L., and King, C. G.: Calcium Distribution in the Blood, *J. Lab. & Clin. Med.* **11**:928 (July) 1926.

6. Walters, W., and Bowler, J. P.: Preoperative Preparation of Patients with Obstructive Jaundice, *Surg. Gynec. Obst.* **39**:200 (Aug.) 1924.

The examinations of the total calcium content of the whole blood, plasma and serum have, in the hands of different workers, yielded variable results in the investigations on jaundice. The workers on the modifying action of calcium salts on the toxicity of bile are not in accord. The proponents of the existence of a deficiency in the available calcium of the blood in jaundice quote with considerable emphasis the work of Kirk and King. With the exception of these authors, this group base their proof for the existence of a calcium deficiency on indirect evidence, such as the purported decrease in the clotting time of the blood of jaundiced patients obtained after therapy with agents that are known to increase the diffusible calcium content of the blood. Since there is a lack of accord, and some of the work goes back as far as 1909, ten years or more before a satisfactory method was developed for the estimation of small amounts of calcium in biologic fluids, it is well at this time to evaluate the reports of such observations.

TABLE 1.—*Results from King and Stewart¹ Purporting to Show Absorption of Calcium by the Bile Pigments Circulating in the Blood Stream*

	Normal Blood*	Blood of Jaundice*	Remarks
I.....	0.050 Gm. calcium	0.060 Gm. calcium	20 per cent increase
II.....	0.045 Gm. calcium	0.053 Gm. calcium	16 per cent increase
		0.060 Gm. calcium	20 per cent increase

* These results are probably expressed as grams of calcium per liter of blood, which would be equivalent to 5 and 4.5 mg. per hundred cubic centimeters, values that are compatible with the established lower values for whole blood.

CRITICAL REVIEW OF THE LITERATURE

In 1909, on the basis of an analysis of the blood calcium in two dogs, King and Stewart¹ concluded that the bile pigments circulating in the blood in obstructive jaundice gradually absorb the calcium of the organs and tissues to form calcium compounds which diminish the amount of available calcium in the tissues. They determined one normal value for the calcium content of the blood in each of two dogs and then tied off the common bile duct. In one case, a single analysis of blood was made after the experimental jaundice was produced, and in the second, two determinations of calcium were made after the jaundice was produced. Since their methods of analysis were not described and they did not show how their results were expressed, it is difficult to survey critically their experimental data (table 1), unless it is assumed that they expressed their values in grams of calcium per liter of blood. This apparently is what they did, for if one assumes that they ashed whole blood of dogs, their normal value could be read as 5 and 4.5 mg. per cent, respectively, and these results would be compatible with the lower values for whole blood of dogs. Conclusions were based on a 20 per cent change in experimental values,

apparently without a consideration of the normal limits of variations in such analyses. It is now well known that whole blood, depending on the volume occupied by the red blood corpuscles⁷ or the hematocrit, as it is now expressed, may vary in man from 5.3 to 6.8 mg. per cent,⁸ by difference, a variation of 28 per cent over the lower value. The range for serum calcium in dogs is close to that found in human beings. The 20 per cent change found by King and Stewart may still be within the normal range of variation and otherwise not be of significance. As the methods for the analysis of small amounts of calcium in biologic fluids were far from satisfactory at that time and up until the publications of Kramer and Howland⁹ in 1920, and of Kramer and Tisdall in 1921¹⁰ and 1922,⁷ the work of King and Stewart remains valuable mainly because of its historical interest. But even as late as 1927, quotations from this work were to be found as argument to justify conclusions that significant alterations in the blood calcium exist in jaundiced patients.¹¹

Observations on the state of the blood calcium in jaundice have been confusing, and the difficulty of interpretation has been increased by the use of the words "ionic" and "ionizable" in describing analytic methods for the determination of the total calcium¹² content of the whole

7. Kramer, B., and Tisdall, F. F.: Distribution of Sodium, Potassium, Calcium and Magnesium Between Corpuscles and Serum of Human Blood, *J. Biol. Chem.* **53**:241, 1922. Rothwell, C. S.: Calcium Determination in Whole Oxalated Blood, *J. Biol. Chem.* **74**:257 (Aug.) 1927. Stewart, C. P., and Percival, G. H.: Calcium in Corpuscles, Plasma and Serum, *Biochem. J.* **22**:548, 1928.

8. Kramer, B., and Tisdall, F. F.: The Direct Quantitative Determination of Sodium, Potassium, Calcium and Magnesium in Small Amounts of Blood, *J. Biol. Chem.* **48**:223 (Sept.) 1921.

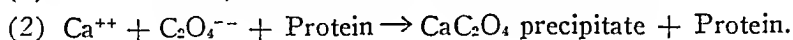
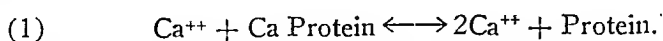
9. Kramer, B., and Howland, J.: Method for Determination of Calcium in Small Quantities of Blood Serum, *J. Biol. Chem.* **43**:35 (Aug.) 1920.

10. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Calcium and Magnesium in Small Amounts of Serum and Plasma, *Bull. Johns Hopkins Hosp.* **32**:44 (Feb.) 1921.

11. Cantarow, A.; Dodek, S., and Gordon, B.: Calcium in Jaundice with Special Reference to the Effect of Parathyroid Extract on Distribution of Calcium, *J. Coll. Phys.* **49**:132, 1927; Calcium Studies in Jaundice, with Special Reference to Effect of Parathyroid Extract on Distribution of Calcium, *Arch. Int. Med.* **40**:129 (Aug.) 1927.

12. The term total calcium is used here to denote the value found on analysis of serum or whole blood, which has stood from 6 to 24 hours, after the addition of a soluble oxalate salt, such as is used in the methods based on the Kramer and Tisdall method for the analysis of serum calcium. For a discussion of the reaction that occurs when calcium is precipitated in serum by the addition of oxalates, consult Stewart and Percival (footnote 8).

blood, the serum or the plasma by procedures such as that described by Vines³ and that recently by Tweedy and Koch.¹³ If calcium exists in the plasma or serum, partly in the ionic form as Ca^{++} ion, and partly in the nonionized form in combination with protein,¹⁴ as there is good reason to believe it does,¹⁵ if sufficient time elapses after the addition of oxalates, the following equation goes completely to the right to form a precipitate of calcium oxalate and unbound protein (relative to calcium).



The result is a precipitation of the total amount of the calcium in the serum, plasma or blood, including the ionic, nonionic and protein-bound. Of this amount, only part is ionic or ionized.¹⁶ The clinician may not always discriminate with ease the refinement in terminology and the difference between calcium bound to protein that is potentially ionizable from calcium that is actually in the ionic form. Those methods which depend on the precipitation of calcium in the serum or blood by the direct addition of oxalates, determine not only the small ionic fraction, but the protein-bound potentially ionizable calcium as well, or the total calcium. Such methods yield values that lie in the average range of from 9 to 11 mg. per hundred cubic centimeters for human beings,¹⁷ with extreme values of from 8.5 to 11.7 mg. per hundred cubic centimeters.¹⁸ The methods of Vines³ and of Tweedy and Koch¹³ furnish values that fall within these ranges. On this, we refer the reader also to Stewart and Percival,⁷ who discussed and criticized the work of Vines and also presented a discussion of the factors which are involved in the precipitation of calcium from serum by the addition of an oxalate solution.

13. Tweedy, W. R., and Koch, F. C.: A Suggested Modification of the Kramer and Tisdall Method for the Microchemical Estimation of Ionizable Calcium in the Blood Plasma, *J. Lab. & Clin. Med.* **14**:747 (May) 1929.

14. Loeb, R. F., and Nichols, E. G.: Effects of Dialysis and Ether Extraction on Diffusibility of Calcium in Human Blood Serum, *J. Biol. Chem.* **74**:645 (Sept.) 1927. Greenberg, D. M.: The Electrical Transference of Calcium in Blood Serum Protein Solutions, *J. Biol. Chem.* **79**:177 (Sept.) 1928.

15. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, *Physiol. Rev.* **8**:283 (July) 1928.

16. Neuhausen, B. S., and Pincus, J. B.: A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, *J. Biol. Chem.* **57**:99 (Aug.) 1923.

17. Myers, V. C.: Practical Chemical Analysis of Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 170.

18. Crippe, L. H., and McElroy, W. S.: Atopy, *Arch. Int. Med.* **42**:865 (Dec.) 1928.

The recent work of Cantarow and his associates¹¹ purported to show that a deficiency of calcium existed in the whole blood of jaundiced patients. Their analyses of whole blood were done by a method of their own,¹⁰ in which they attempted to determine the total calcium of whole blood by the direct oxalate precipitation of laked blood, without first removing the cellular débris or the proteins. Their values given as from 6.5 to 9.5 mg. per hundred cubic centimeters are high when compared with the accepted values of from 5.3 to 6.8 mg. obtained by Kramer and Tisdall.⁸ The latter figures for whole blood have been confirmed both by Rothwell²⁰ and by Stewart and Percival.⁷ Rothwell pointed out the necessity of removing the cellular detritus of whole laked blood before the calcium could be determined in the presence of protein. By the method of Caven and Cantarow,¹⁹ a small precipitate of cellular detritus was thrown down with the calcium oxalate precipitate. This caused their results to be higher than any reported by the other accepted methods for whole blood, but they felt that their error was a constant one and that their results were comparable within their own standard for normal values.

In analyses of whole blood for calcium done according to their method and of plasma and serum done by a standard procedure, after the injection of parathyroid hormone, they obtained, on the same patient, a parallel change in the whole blood and plasma calcium values without a similar type of change in the serum calcium value. Since it has been amply demonstrated that the plasma and serum calcium values are identical when the ordinary concentration of anticoagulants is used to obtain the plasma, and that the red blood cells contain insignificant amounts of calcium,⁷ it is difficult to harmonize such divergent observations. As Cantarow and his co-workers themselves called attention to the fact that their method for whole blood utilized a standard for the normal that was valuable only when the results of the method were compared with its own standard, a comparison of values utilizing widely different standards for the normal values offers itself as a possible explanation for their divergent results. Yet these authors drew their conclusions that the wide variations in the whole blood calcium as opposed to the relative fixation of the serum calcium must be dependent largely on the varied amounts of functionally available and diffusible fractions of the calcium and on the bile pigments that bind the calcium fraction and are excreted in the urine.

In consideration of the factors enumerated, the conclusions reached by Cantarow and his associates, that a deficiency exists in the available

19. Caven, W. R., and Cantarow, A.: A Method for the Determination of Calcium in Whole Blood, *J. Lab. & Clin. Med.* **12**:76 (Oct.) 1926.

20. Rothwell, C. S. (footnote 7, second reference).

and diffusible calcium of the blood in patients with jaundice, cannot be accepted as proved.

Analysis of Diffusible Calcium in Jaundice.—The improvements²¹ in the method of Moritz²² for the determination of the diffusible calcium of the blood serum has placed in our hands a more exact method for the determination of the state of the available calcium than can be offered by analysis of the total calcium of the serum, plasma or whole blood. It has been indicated by Neuhausen and Pincus¹⁶ and Stewart and Percival⁷ that the water-clear, protein-free ultrafiltrate contains the same concentration of ionic calcium as the blood serum, but all the ultrafiltrate is not ionized. Various workers have shown that the analysis for diffusible calcium of the blood serum, which normally varies between extremes of 4.2 and 6.8 mg. per hundred cubic centimeters of the ultrafiltrate, is a better measure of the physiologically available calcium than the analysis for total calcium.²³

The utilization of the analysis for ultrafiltrable calcium in the study of the state of the calcium in jaundice has to our knowledge been attempted only by Kirk and King.⁵ On the basis of four analyses in the case of apparently normal persons, they found that the diffusible calcium constituted from 70 to 75 per cent of the total calcium of the serum with an average value of 72.3 per cent. This range is much higher than that given by other authors,²⁴ whose figures usually show between 45 and 55 per cent of the serum calcium to be diffusible. In jaundice, they found that only 55 per cent of the calcium was diffusible as against the 72 per cent which they considered as normal. A critical examination of their data, table 2, reveals changes that are apparent rather than actual. They are apparent because the values of ultrafiltrable calcium were expressed in terms of percentage of the total calcium. If the values of the ultrafiltrable calcium are recalculated to be expressed similarly in terms of concentration, it will be seen that their data do not show alterations in the concentration of the diffusible calcium significant enough to be outside the region of normal variation. Their

21. Greenberg, D. M., and Gunther, L.: On the Determination of Diffusible and Nondiffusible Serum Calcium, *J. Biol. Chem.* **85**:491 (Jan.) 1930.

22. Moritz, A. R.: The Effect of Ultraviolet Radiation on the State of the Serum Calcium, *J. Biol. Chem.* **54**:81, 1925.

23. Stewart and Percival (footnote 15); Moritz (footnote 22); Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, *J. Clin. Investigation* **5**:259 (Feb.) 1928.

24. Greenberg and Gunther (footnote 21); Liu (footnote 23, fourth reference); Updegraff, H.; Greenberg, D. M., and Clark, G. W.: A Study of the Distribution of the Diffusible and Nondiffusible Calcium in Blood Sera of Normal Animals, *J. Biol. Chem.* **71**:87 (Dec.) 1926.

low values for the total calcium in jaundice are in agreement with our results. We will show later that such values are due to a fall in the nondiffusible fraction of the calcium which may be explained by a decrease in the serum proteins.

Updegraff, Greenberg and Clark²⁴ pointed out that the usual procedure of reporting the value of the diffusible calcium in terms of percentage of the total serum calcium may be misleading; for the diffusible calcium has, in a normal person under a given condition, a practically fixed value, whereas the concentration of the nondiffusible calcium fluctuates within comparatively wide limits. The value of the diffusible

TABLE 2.—*Results by Which Kirk and King⁵ Purported to Show a Low Diffusible Calcium in Jaundice**

Total Calcium Mg. per 100 Cc. Serum	Percentage,		Calculated Diffusible Calcium, Mg. per 100 Cc.	Remarks
	Ultrafilterable Calcium	Total Calcium		
8.49		67.4	5.7	Normal
7.58		67.7	5.2	Normal
9.24		80.9	7.5†	Normal
7.43		72.3	5.3	Normal
9.80		45.95	4.5	Jaundice
11.39		55.1	6.3 (serum)	Jaundice
7.86		66.5	5.2	Jaundice
4.31 (?)		59.6	2.2 (serum)†	Jaundice
6.04		59.9	4.1 (serum)	Jaundice
7.91		64.0	5.0	Jaundice
8.52		48.2	4.1 (serum)	Jaundice
7.49		53.5	4.4	Jaundice

* They attempted to obtain the diffusible calcium of whole blood by the use of an organic anticoagulant, but in certain instances clotting occurred, and the diffusion was continued on serum without altering the final results. The values reported as percentage of the total serum calcium as shown by the ultrafilterable calcium, indicated apparent changes in jaundice. The same data recalculated, as in the third column, with one exception, showed the concentration of the diffusible calcium to be within the limits reported for the normal. The data also show two irregular results compatible with inconstant collodion membrane preparations.

† A very high value for the normal. Most likely the error here was the leakage of serum through the collodion membrane.

‡ This value is extremely low, and was probably due to an impermeable membrane. No mention was made of tetany.

calcium expressed in terms of percentage of the total serum calcium will therefore fluctuate and create an impression that it is undergoing a change when this may not be the case. On the other hand, the value of the diffusible calcium when expressed in terms of concentration of calcium in the ultrafiltrate will not show these apparent changes. Liu,²³ in his studies on chronic juvenile tetany, demonstrated the clinical importance of expressing the value of the diffusible calcium in terms of concentration rather than as a percentage of the total calcium. The diffusible calcium in tetany varied within a narrow range between 3.1 and 3.4 mg. per hundred cubic centimeters, while the total calcium of the serum of the same specimens varied between 6.5 and 9 mg. per hundred cubic centimeters, as the result of variations in the nondiffusible fraction. The average value in tetany could be expressed as 50 and 36 per cent,

respectively, of the total serum calcium and thus show wide changes that were not actually present. The stability of the concentration of diffusible calcium for a given condition has also been shown in our own studies on parathyroid tetany, in which a similar fixation of the diffusible calcium at a low level was found accompanying large variations in the total calcium due to fluctuations in the nondiffusible calcium fraction.

If one recalculates the data of Kirk and King⁵ (table 2) to express their results in terms of concentration of calcium in the ultrafiltrate rather than in terms of percentage of the total serum calcium, it can be seen that in seven of eight jaundiced patients (including two with values of 4.1 mg.) the concentration of the diffusible calcium falls within the normal range of 4.2 and 6.8 mg. per hundred cubic centimeters. One value is obviously incorrect, being so low that it would be compatible only with the existence of tetany. It may be safely stated from the values reported for juvenile tetany by Liu²³ and from our studies on parathyroid tetany that values for the diffusible calcium below 3.4 mg. per hundred cubic centimeters (unless one is dealing with poor collodion membrane preparations) are accompanied either by acute or chronic symptoms of tetany. Kirk and King made no mention of such symptoms, and it may be safely assumed that such symptoms were not present.

A further perusal of table 2 reveals wide deviations in certain of their analyses, which probably indicates inconstant action in the collodion membranes used. We have pointed out²¹ that variable results, either values too high owing to serum leaking through the membrane (their value of 7.5 mg. per hundred cubic centimeters for one of their normal persons may be due to this cause) or values too low owing to failure of the membrane to permit diffusion (their low results of 3.4 and 2.5 mg. per hundred cubic centimeters in the absence of symptoms of tetany, are of this type), will be obtained if the collodion mixture is not proper. We have suggested a formula for collodion, or a collodion preparation that allows a constant ultrafiltration to be obtained.²¹

A critical review of the results of Kirk and King⁵ shows that the concentration of the diffusible calcium in the serums of six of eight patients with jaundice is within the normal range of variation. The results of the investigations by Kirk and King into the state of the diffusible calcium in jaundice fail to show significant alterations from the normal values for the concentration of the ultrafiltrable calcium of the blood of jaundiced patients.

The Detoxification of Bile Pigments by Calcium Salts.—A second method of approach by which it has been deduced that a deficiency of calcium exists in the blood of jaundiced patients has been through observations on the delayed coagulation of blood in vitro after the addition of bile;¹ or through observations on the antagonistic action of

calcium salts on the delay in coagulation occasioned by the addition of bile,² and by the observations on the coagulation of blood after the injection of bile pigment into the circulation, with or without a preliminary treatment with calcium salts to effect a detoxification of the bile.¹

The experimental results in the detoxification of bile and bile salts by the action of soluble calcium salts are not in agreement. Meltzer and Salant²⁵ as early as 1905 pointed out that confusion of results was obtained in the in vivo injection of bile, depending on the rate of injection and the concentration of the bile entering the blood stream. Even Lee and Vincent,² who supported the view that in the in vitro experiments soluble calcium salts in weak concentrations have an antagonistic action on the delayed clotting time occasioned by the addition of bile to blood, pointed out that bile also affected other elements involved in coagulation. Recently, Emerson²⁶ reinvestigated the results of the experiments with in vivo injection and found that soluble calcium salts had no appreciable detoxifying effect on bile, and concluded that the beneficial effects of the administration of calcium chloride in obstructive jaundice as a preoperative preparation are due to effects other than its action as a detoxifying agent.

Shortening of Coagulation Time by Therapy Aimed at Increasing the Blood Calcium.—A deficiency of calcium in the blood of jaundiced patients has also been claimed because of the effect of calcifying agents on the coagulation time. This method of approach to the problem has been through observations of the action of soluble calcium salts in jaundiced patients in whom there was present a delay in coagulation time. It has been claimed that such therapy shortens the clotting time in jaundiced patients²⁷ and reduces the operative mortality⁶ when used as a preoperative measure in patients with obstructive jaundice. Calcium chloride and parathyroid extract have also been found to be of value in controlling hemorrhages from various causes.²⁸

Conclusions based on such evidence must necessarily be indirectly arrived at because there is little, if any, experimental proof of the actual existence of a deficiency of available calcium. Such conclusions are furthermore open to objection because it has been claimed that

25. Meltzer, S. J., and Salant, W.: Studies on the Toxicity of Bile, *J. Exper. Med.* **7**:280, 1905.

26. Emerson, W. C.: The Effect of Calcium Chloride on the Toxicity of Bile, *J. Lab. & Clin. Med.* **14**:714 (May) 1929.

27. Walters, W.: Preoperative Preparation of Patients with Obstructive Jaundice, *Surg. Gynec. Obst.* **33**:651 (Dec.) 1921.

28. Vines (footnote 3): Walters (footnote 27); Gordon, B., and Cantarow, A. J.: Use of Parathyroid Extract in Hemorrhage, *J. A. M. A.* **88**:1301 (April 23) 1927.

soluble calcium salts injected into the blood stream may temporarily shorten the coagulation time even in normal persons.²⁹ Zimmerman³⁰ recently reinvestigated the effect of an increase in the total blood calcium obtained through the injection of parathyroid hormone in jaundiced and nonjaundiced dogs and human beings. He did not find a decrease in the clotting time in either condition concomitant with the increase in the blood calcium and concluded that calcium salts per se do not shorten the coagulation time in jaundice. Similar results were obtained by one of us in jaundiced and nonjaundiced patients, by the use of Walters and Bowler's⁶ regimen of calcium chloride administration as a preoperative measure.³¹ The contention that the administration of calcium salts as a preoperative measure shortens the coagulation time cannot be accepted as proved. If this is true, its corollary, that there is a deficiency of calcium in jaundice, likewise must be viewed with suspicion. Recent workers are tending toward this view, as shown by the remarks of Ravdin,³² who also could find no evidence of alterations in the calcium fractions of the blood serum in human beings and in dogs with jaundice.³³ He and Morrison also studied the coagulation time in jaundiced patients by the Lee and White method and came to the conclusion that the reduction in coagulation time frequently observed during the preoperative preparation of the patient and the fewer postoperative hemorrhages were due to the dextrose used previous to the operation rather than to the calcium salts. They demonstrated, in their own experiments, a marked reduction in the coagulation time of the blood of the jaundiced and nonjaundiced patients and dogs after the intravenous administration of a solution of dextrose. That the intravenous injection of calcium salts causes a similar phenomenon has never been definitely shown in the literature.

Brougher³⁴ used the therapeutic method of approach to determine the state of the diffusible calcium of the blood in jaundice. He did not analyze the blood of his animals for the concentration of the ultrafiltrable calcium, but argued from a decrease in clotting time following

29. Coleman, C. J.: The Coagulation of Blood and the Effect of Certain Drugs and Toxins upon It, *Biochem. J.* **2**:184, 1907.

30. Zimmerman, L. M.: Effect of Parathyroid Hormone on Blood Coagulability. With Special Reference to Jaundice, *Am. J. M. Sc.* **174**:379 (Sept.) 1927.

31. Unpublished work done at the Kaspars Cohn Hospital, Los Angeles, with the assistance of Dr. J. R. Lacoe.

32. Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Diseases, *J. A. M. A.* **93**:1193 (Oct. 19) 1929.

33. No data were given regarding the results of their analyses for calcium.

34. Brougher, J. C.: The Effect of Cod Liver Oil on the Delayed Coagulation Time Following Experimental Obstructive Jaundice, *Science* **68**:256, 1928.

the administration of cod liver oil to jaundiced dogs that the diffusible calcium was at fault. Liu,³⁵ he pointed out, showed that cod liver oil increased both the fractions of the serum calcium, the diffusible and the nondiffusible, the former being increased more than the latter. From this fact Brougher argued that it was rational to use cod liver oil to hasten coagulation of the blood "in jaundiced animals in which diffusible or available calcium is low"; thus he stated as a fact an assumption which had yet to yield to experimental proof, for till then no actual work had been done outside of the observations of Kirk and King,⁵ discussed heretofore, on the analysis for the ultrafiltrable calcium of the blood in jaundice.

Brougher concluded that the efficacy of cod liver oil in causing the shortening of the clotting time in jaundice that he observed was probably based on its ability to increase the ionizable calcium. Since there is at present no satisfactory method for the determination of ionized calcium, one can do little else but conjecture as to the variations of ionic calcium under cod liver oil therapy. But the condition of the diffusible calcium in jaundice is susceptible of experimental proof, and pure conjecture based on indirect observation is not permissible. The results of our experiments and observations on the state of the diffusible calcium in jaundice will now be stated.

EXPERIMENTAL PROCEDURE

Our studies were made on eleven adults who were jaundiced from various causes. In every case in which it was practicable, studies were made on the total and diffusible calcium of the serum, the inorganic phosphate of the serum, the serum albumin and globulin, the serum icteric index and the bleeding time (Duke) and the clotting time of the blood. Generally, 20 cc. of blood was collected for analysis from the cubital vein of the arm, in the morning after a fast of one night. Moderate stasis was employed by means of a tourniquet. A large needle, gage 19, was used to ensure rapid collection of the specimen. The serum was removed within from four to twelve hours after the specimen was collected. We have found²¹ that no change in the total and diffusible calcium can be detected even after twenty-four hours, if the serum is allowed to stand in contact with the clot in a tightly stoppered tube.

The general procedure was to use, in the following order, 2 cc. of serum for the determination of total calcium, 0.5 cc. for that of the serum proteins, 4 or 5 cc. for ultrafiltration, and 2 cc. for the determination of inorganic phosphate. The inorganic phosphate determination was not set up until we were satisfied that 4 or 5 cc. of serum was available for filling the collodion membrane³⁶ for ultra-

35. Liu, S. H.: The Partition of Serum Calcium into Diffusible and Non-Diffusible Portions, *Chinese J. Physiol.* **1**:331 (July) 1927.

36. The preparation of the collodion membrane is of the utmost importance. We have reported elsewhere (footnote 21) the method for the preparation of satisfactory membranes.

filtration. If the amount of serum that remained was insufficient to allow 2 cc. for the determination of inorganic phosphate, this analysis was performed on the supernatant fluid obtained from the first centrifugation of the total calcium precipitate, according to the method described by ourselves.³⁷ (If the total amount of serum available does not amount to more than 3 or 4 cc. the system of analysis discussed elsewhere by the authors [footnote 21] can be used to give results satisfactory for clinical usage.) The icteric index, bleeding time and clotting time were found independently within a short time of the drawing of the specimen for analysis.

Methods.—The analyses for total calcium were done on the serum by Tisdall's modification³⁸ of the Kramer and Tisdall method.³⁹ The ultrafiltrate was analyzed for diffusible calcium by the same method, modified, however, by the authors²¹ to prevent the loss of crystals that might float on the protein-free fluid after the centrifugation. The final analyses were done, in most instances, according to the gasometric method of Van Slyke and Sendroy.⁴⁰ A few samples of total and diffusible calcium were titrated with five thousandths-normal potassium permanganate, freshly diluted from a tenth-normal or a hundredth-normal solution. We have checked the titration against the gasometric procedure and when employing samples with calcium equivalent to that in 2 cc. of normal blood serum, have obtained agreement within the error of the titration method, and often to 1 or 2 per cent. The serum was analyzed for proteins by the colorimetric method of Greenberg.⁴¹ The bleeding time was found according to the method of Duke,⁴² and the clotting time by the method of Lee and White.⁴³ The icteric index was determined by the usual procedure. All analyses for phosphate were based on the Fiske and Subbarow method.⁴⁴

The experimental data are shown in table 3. Although we have expressed the concentration of the diffusible calcium as per hundred cubic centimeters of serum, we have found that it does not matter whether the nondiffusible fraction is obtained by separate analysis of the concentrate that remains in the bag after ultrafiltration is completed, or by the subtraction of the value for the calcium of the ultrafiltrate from the value for the total serum calcium. Within the limits of error of our methods of analysis, the concentration of calcium in the ultrafiltrate is the concentration of the diffusible calcium of the serum, for the calcium in the

37. Gunther, L., and Greenberg, D. M.: A Note on the Determination of the Inorganic Phosphate of the Serum on the Filtrate from Calcium Analysis, *J. Biol. Chem.* **82**:551 (May) 1929.

38. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for Determination of Calcium in Small Amounts of Serum, *J. Biol. Chem.* **56**:439 (June) 1923.

39. Kramer, B., and Tisdall, F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, *J. Biol. Chem.* **47**:475 (Aug.) 1921.

40. Van Slyke, D. D., and Sendroy, J., Jr.: Gasometric Determination of Blood Calcium, *Proc. Soc. Exper. Biol. & Med.* **24**:167 (Nov.) 1926.

41. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, *J. Biol. Chem.* **83**:545 (May) 1929.

42. Todd, T. C.: *Clinical Diagnosis by Laboratory Methods*, ed. 5, revised, Philadelphia, W. B. Saunders Company, 1924, p. 251.

43. Lee and White, in Todd, T. C.: *Clinical Diagnosis by Laboratory Methods*, ed. 5 revised, Philadelphia, W. B. Saunders Company, 1924, p. 248.

44. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375 (Dec.) 1925.

TABLE 3.—Jaundice Studies

Patient	Calcium*		Inor- ganic Phos- phate*	Albu- min*	Glob- ulin*	Bleeding Time, Minutest	Clotting Time, Minutest	Icteric Index	Duration of Jaundice	Remarks
	Total	Dif- fusible								
<i>Group with abnormal bleeding and clotting time</i>										
Rey.	9.3	5.5	3.8	11.0	100	18 days	Catarrhal jaundice; Kahn test on the blood, 1 plus
Cant.	8.0	4.9	3.1	3.4	2.9	...	13.5	100	Toxic jaundice, bronchopneumonia, hyperplasia of thyroid (exophthalmic goiter)
Bles.	8.1	4.5	3.6	5.0	17.5 25	14 days	Primary carcinoma of cecum, secondary in the liver; fragility of red blood cells from 0.4 to 0.25%
Fras.	7.8	5.1	2.7	3.6	2.6	2.5	15.0	50	3 months intermittent	Carcinoma of ampulla of Vater; nosebleeds; 10 cc. of 5% calcium chloride was administered intravenously daily for three days before the samples of blood were taken; the nosebleeds continued; jaundice was complete for one week before this specimen was taken
Bobe.	10.0 10.0	5.3	4.7	9.5 9.0	8.0 7.0	133	7 months intermittent	Carcinoma of bile duct; second bleeding and clotting time fourteen days after adequate cholecystgastrostomy
<i>Group with normal bleeding or clotting time.</i>										
Colv.	7.0	4.7	2.4	3.8	1.7	...	6.5	25	7 days	Toxic jaundice; B. welchii infection of skin following enterostomy for intestinal obstruction
Swe.	8.6	4.5	3.1	3.5	2.3	2.5	3.5	200	21 days	Carcinoma of head of the pancreas
Trau.	9.4	5.5	3.9	4.6	1.3	4.75	3.0#	33.5	Congenital familial hemolytic jaundice; fragility of red blood cells; maximum, 0.65%; minimum, 0.45%
Dorn.	10.5	5.4	5.1	3.5	5.8#	200	Not recorded	Portal cirrhosis of the liver?
Mars.	9.2	6.4	2.8	60	2-3 days	Carcinoma of the head of the pancreas
Wright.	10.3	5.0	1.5	4.0#	17	Postoperative convalescence from obstructive jaundice; patient had barely noticeable conjunctival icterus

* All values in milligrams per hundred cubic centimeters of serum.

† By the method of Duke (in Todd, footnote 42).

‡ By the method of Lee and White.⁴³

§ All cases from the records of the University of California Hospitals, San Francisco, Calif.

By capillary tube.

concentrate remaining after ultrafiltration is completed, plus the calcium that diffuses through the membrane equals the concentration of the total calcium of the serum, as may be expressed in the following equation.²¹

$$T_{ca} = \left[\frac{a-x}{a} \right] C_{ca} + \left[\frac{x}{a} \right] F_{ca}$$

T_{ca} , C_{ca} and F_{ca} are the symbols for total calcium, concentrate calcium, and ultrafiltrate calcium in milligrams per hundred cubic centimeters or other appropriate units; a is the cubic centimeters of serum introduced into the collodion sac, and x is the amount of fluid obtained in the ultrafiltration.

RESULTS

The Diffusible Calcium.—The lowest concentration of diffusible calcium found in the blood of jaundiced patients was 4.5 mg. per hundred cubic centimeters and the highest value was 6.4 mg. per hundred cubic centimeters with an average value of 5.16 mg. A study of forty-two analyses on twenty-four medical students and staff members, all apparently in good health, showed variations between 4.2 and 6.8 mg. per hundred cubic centimeters with an average of 4.96 mg. The average for eleven jaundiced patients was 5.16 mg. per hundred cubic centimeters against 4.96 mg. per hundred cubic centimeters for the group of forty-two analyses on apparently healthy medical students, which may serve as the normal measuring rod. Chart 1 shows in a striking manner how the values for the jaundiced patients fall within the zone of the variations found in the normal group.

It appears from this data that a demonstrable deficiency of calcium does not exist in the blood of jaundiced patients as determined by measuring the diffusible calcium of the serum.

The Nondiffusible Calcium.—In jaundiced patients, the nondiffusible calcium of the blood varied from 2.4 to 5.1 mg. per hundred cubic centimeters with an average of 3.68 mg. The nondiffusible calcium in forty-two analyses on medical students and staff members varied between 4.1 and 7.2 mg. per hundred cubic centimeters with an average of 5.07 mg. The zone of variation of the nondiffusible calcium of the blood of jaundiced patients lies well below the zone of variation found for the nondiffusible calcium of apparently normal persons, with an average of 3.68 mg. per hundred cubic centimeters for the jaundiced patients as against an average of 5.07 mg. per hundred cubic centimeters for the medical students. The difference is again shown strikingly in chart 2. These observations, of course, indicate that the average total calcium value of the blood of the jaundiced patients is low, since the sum of the diffusible and the nondiffusible calcium equals the total calcium content of the serum. But this cannot be interpreted as proof for the existence of a deficiency in the available calcium of the serum.

Recent work in the field of diffusible calcium by Stewart and Percival ⁴⁵ and by Liu ⁴⁶ indicates that the diffusible calcium rather than the total calcium is a better index of the physiologically active or available calcium. Our data do not show a deficiency in the diffusible calcium in jaundiced patients. The discrepancy between the apparent deficiency

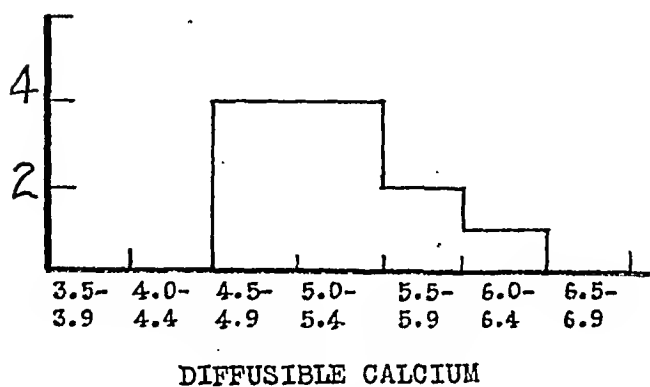
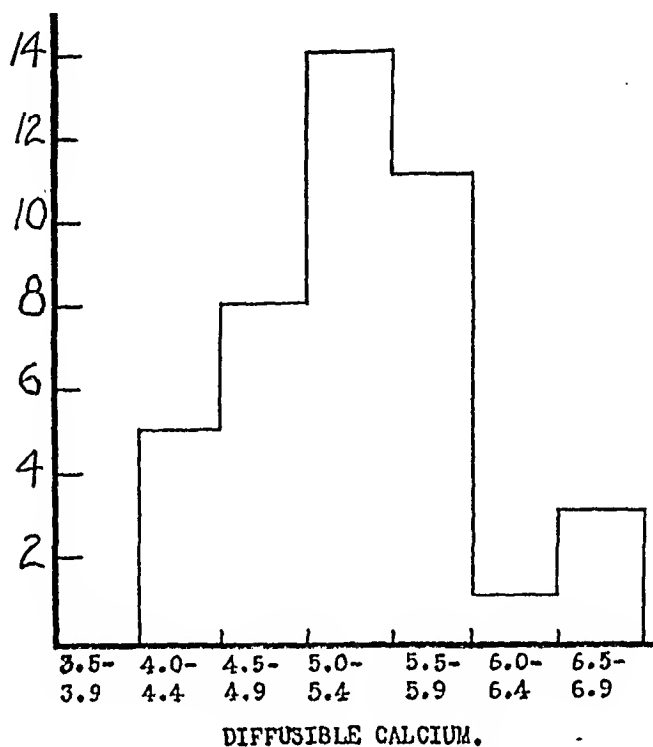


Chart.1.—The variation of the concentration of the diffusible calcium in blood serum in forty-two analyses on apparently normal medical students and staff members, University of California Medical School, upper; in jaundice, lower. Values in milligrams of calcium per hundred cubic centimeters of serum.

of calcium in the blood of jaundiced patients as seen by the values for total calcium, and the abundance of physiologically available calcium as

45. Stewart and Percival (footnotes 8 and 15).

46. Liu (footnote 23, fourth reference, and footnote 35).

demonstrated by the values for diffusible calcium serves to emphasize again, as pointed out by Updegraff, Greenberg and Clark²⁴ and Liu,⁴⁶ that the values for the diffusible calcium of the serum are independent of the values for the total calcium, and serve as a better index of the state of the calcium of the serum. The fluctuations which make the difference in percentage of total calcium shown by the diffusible calcium

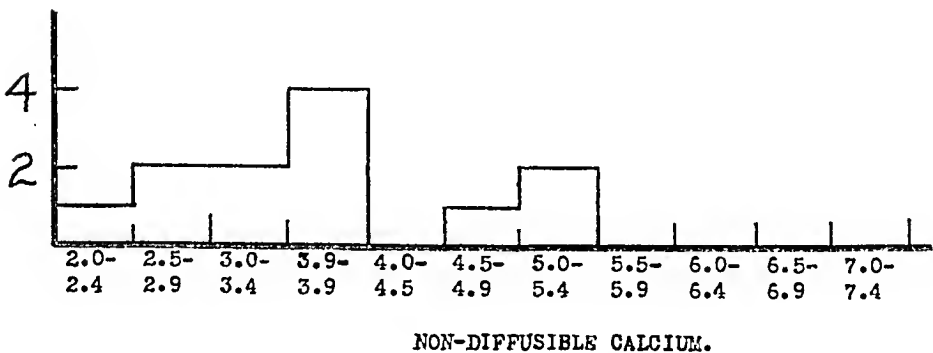
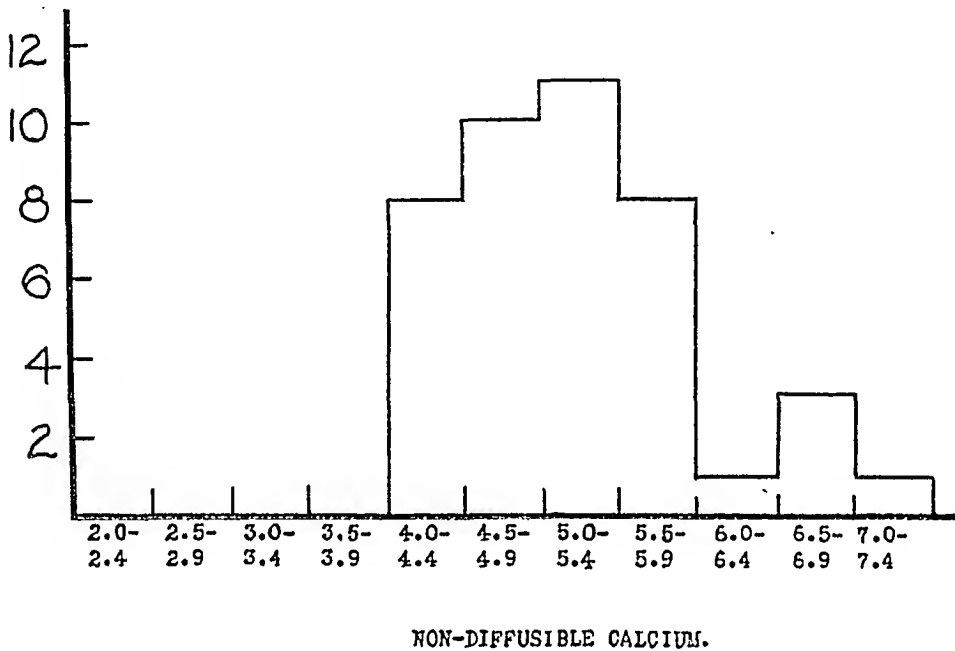


Chart 2.—The variation of the nondiffusible calcium in blood serum in apparently normal medical students and staff members, University of California Medical School, upper; jaundice, lower. Value in milligrams of calcium per hundred cubic centimeters of serum.

in a given person occur in the nondiffusible calcium, which may fluctuate normally over a wide range, while the level of diffusible calcium remains little changed.

The importance of the concentration of the diffusible calcium is nicely demonstrated in diseases known to be due to a deficiency in cal-

cium metabolism. Such diseases as infantile tetany and tetany caused by a deficiency of parathyroid hormone show a diffusible calcium that drops to 3 mg. per hundred cubic centimeters or lower, while the total calcium (due to fluctuations in the nondiffusible calcium) may vary at the same time between 6 and 9 mg. per hundred cubic centimeters. The increase in the nondiffusible calcium, however, shows no effect in the amelioration of the clinical symptoms as long as the diffusible calcium remains low. Now, if there were a deficiency of available calcium in jaundice, one would look for a decrease in the ultrafiltrable calcium such as one finds in diseases that are known to be accompanied by a deficiency in serum calcium. But such a condition was not found in our series of jaundiced patients. The concentration of the diffusible calcium varied between the same limits as observed in forty-two analyses on apparently normal medical students. The nondiffusible calcium, however, was low, and the low values observed were accompanied by a decrease in the values for the serum albumin in the same patient.

The Serum Proteins.—The low nondiffusible calcium observed in our patients with jaundice can qualitatively, at least, be explained by the low serum albumin (table 3). We have observed an analogous fall in the nondiffusible calcium in nephrosis and in other nonhemorrhagic conditions in which there was a marked reduction in the serum proteins. The serum albumin in the jaundiced patients varied between 3.4 and 4.6 mg. per hundred cubic centimeters, with an average of 3.75 mg. Twelve analyses on medical students showed variations between 4.2 and 5.8 mg. per hundred cubic centimeters, with an average of 4.93 mg. per hundred cubic centimeters, and thirteen analyses on adults in whom there was no reason to suspect a deficiency in the serum proteins revealed variations between 4 and 5.9 mg. per hundred cubic centimeters, with an average of 4.85 mg. Rowe,⁴⁷ who employed the microrefractometric method of Robertson, found the albumin to vary between 4.6 and 6.7 mg. per hundred cubic centimeters. These observations indicate that the serum albumin in our jaundiced patients was definitely low. If one takes this in conjunction with the obtained average value of 3.68 mg. per hundred cubic centimeters for nondiffusible calcium in the cases of jaundice and 5.07 mg. per hundred cubic centimeters for normal adults, there seems to be a clear connection between the low values of serum albumin and the low values of nondiffusible calcium in these patients. The connection seems valid in spite of the rather few analyses for serum proteins in jaundice presented in our data.

47. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum in Health, Syphilis, Pneumonia and Certain Other Infections with the Bearing of Globulin on the Wassermann Reaction, *Arch. Int. Med.* **18**:455 (Oct.) 1916; cited by Myers, V. C.: *Practical Chemical Analysis of Blood*, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 161.

The serum globulin was unchanged in the jaundiced patients. The values varied between 1.3 and 2.9 mg. per hundred cubic centimeters with an average of 2.16 mg. Eleven analyses on medical students and on thirteen apparently normal adults varied respectively between 1.3 and 2 and 1.4 and 2.5 mg. per hundred cubic centimeters, with averages of 2.05 and 2.25 mg., respectively. Rowe's figures were from 1.2 to 2.3 mg. per hundred cubic centimeters, and are comparable with our figures.

The finding of low serum albumin (and low total protein) in all of the jaundiced patients, who also showed low nondiffusible calcium, and therefore low total calcium, is particularly significant, for it has a direct bearing on the present theories on which are based the assumptions that in the blood of patients with jaundice the available calcium is decreased to form nonavailable calcium, or an increase in the protein-bound or bile-protein-bound calcium.

Theories of the Rôle of the Calcium, Protein and Pigment in Jaundice.—King and Stewart,¹ on finding what they thought was an increase in the blood calcium in jaundice, assumed, as an explanation, that the blood calcium united with the bile pigments to detoxify them and was thereby removed as available calcium in its rôle of maintaining the normal bleeding and clotting phenomena. Other workers, Walters and Bowler,⁶ Cantarow and his associates,¹¹ accepting this hypothesis, put forth somewhat modified but similar views and implied, in addition, that the blood calcium then decreased owing to the removal of calcium by the bile pigments.

Kirk and King⁵ modified the conception of King and Stewart¹ by tentatively accepting the hypothesis that some of the calcium was bound to the blood proteins, and in jaundice disturbances in the protein balance might affect the degree of diffusibility of the serum calcium. According to this assumption, the diffusible calcium should decrease and the nondiffusible calcium, in turn, increase by becoming bound to protein. Walters and Bowler⁶ compromised on these views by stating that the pigment becomes fixed to the plasma proteins to some extent, lessening the diffusibility of the pigment molecule and preventing its excretion. The protein pigment combination uniting with calcium then increases the ratio of protein-bound to free calcium, altering the normal diffusibility and ionic relations. According to this assumption, when the degree of icterus becomes high, the pigment protein combination uniting with the diffusible calcium should decrease this form of the serum calcium, and proportionately increase the nondiffusible form.

We found in our analyses that the bile pigments do not diffuse through the collodion membrane, but remain behind with the proteins. This fact alone places in our hands a particularly effective method of

approach to the determination of the validity of the hypotheses which would bind calcium with bile pigments as jaundice increases, to form nonavailable calcium, or the hypothesis which would bind protein with the diffusible calcium as jaundice increases, or would bind the bile protein combinations with diffusible calcium, each to increase the non-diffusible calcium as jaundice increases. A simple analysis of the concentrate for the proteins and the nondiffusible calcium remaining behind after ultrafiltration would either directly support or refute these assertions. Thus, aside from the actual analysis for the concentration of the diffusible calcium of the blood serum in jaundice, the theories on which are based the assumptions of a deficiency in available calcium lend themselves directly to experimental proof.

In the case "Trau," an analysis of the concentrate in the bag revealed a nondiffusible calcium of 3.72. mg. per hundred cubic centimeters. The nondiffusible calcium obtained by difference was 3.85 mg. per hundred cubic centimeters. These values check within the experimental error of the method.⁴⁸ "Trau's" nondiffusible calcium accompanied an icterus which gave a value of 33.5 by the icteric index, and showed a concentration of 3.72. mg. per hundred cubic centimeters, whereas "Swe" with a concentration of pigment which gave an icteric index of 200 showed only 3.05 mg. of nondiffusible calcium per hundred cubic centimeters. These direct experimental observations certainly do not support the hypothesis that an increase in bile pigment decreases the diffusibility of calcium, or binds it in such a fashion as to increase its nondiffusibility. An analysis of the concentrate for its serum proteins gave, in a similar fashion, values identical with the values found in the unconcentrated serum, and no increase in serum proteins was found as the degree of jaundice increased. On the contrary, the serum proteins became low (although there was no direct relation to the severity of the jaundice) owing to a decrease in serum albumin, or were normal. These observations do not confirm the hypothesis that the increasing degree of jaundice binds additional proteins, for the increase in pigment did not increase the serum proteins. The aforementioned results also fail to confirm the assumption that the bile protein combination reduces the diffusibility of calcium by increasing the nondiffusible portion. The nondiffusible fraction by actual analysis and by difference was either normal or low, depending, qualitatively at least, on the serum albumin content.

48. Similar analyses on other patients have shown that the values for the non-diffusible calcium could be arrived at either by subtraction of the values for the diffusible calcium from the values for the total calcium or by an actual analysis of the concentrate. The values obtained by either method agreed within the experimental accuracy of our analytic procedures.

SUMMARY

A critical review of the literature does not reveal sufficient evidence on which to base the conclusion that there exists in the blood of jaundiced patients a deficiency of available calcium, nor is there direct experimental or analytic proof of the existence of a deficiency in the diffusible calcium of the serum.

We have found that the diffusible calcium in the blood of jaundiced patients varies between 4.5 and 6.4 mg. per hundred cubic centimeters. The average value for diffusible calcium in the blood of our jaundiced patients was 5.16 mg. per hundred cubic centimeters as against 4.96 mg. per hundred cubic centimeters determined by forty-two analyses on medical students and staff members who were in good health.

The nondiffusible calcium of the blood of our jaundiced patients varied between 2.4 and 5.1 mg. per hundred cubic centimeters, with an average of 3.68 mg., as compared with variations of 4.1 and 7.2 mg. per hundred cubic centimeters, with an average of 5.07 mg. in apparently healthy medical students. The fall of the nondiffusible calcium was accompanied by a drop in the serum albumin, and can be accounted for, qualitatively, at least, by the decrease in the total serum proteins. The fall in the nondiffusible calcium in certain of the patients cannot be interpreted as a deficiency of available calcium, since ample work in other laboratories, as well as in our own indicates that it is the diffusible fraction of the serum calcium rather than the nondiffusible fraction that is the best measure of physiologically available calcium.

The concentration of the diffusible calcium of the serum remained within the average limits of variation regardless of the degree of jaundice. The nondiffusible calcium was low in four of five patients with a low serum albumin and did not fluctuate in proportion to the degree of jaundice. The total serum proteins did not increase with increasing degrees of jaundice. Our analytic data do not support the hypotheses set forth; namely, the hypothesis of King and Stewart¹ that calcium salts unite with bile pigments to detoxify them and are thereby removed as available calcium; the hypothesis of Kirk and King⁵ that in jaundice a disturbance occurs in the protein balance which decreases the degree of diffusibility of calcium; and the hypothesis of Walters and Bowler⁶ that the bile pigment becomes fixed to the plasma proteins and the protein pigment combination then unites with calcium to increase the ratio of protein-bound to free calcium, thus altering the normal diffusibility of calcium.

CONCLUSIONS

1. The indirect method of calcium replacement therapy in jaundice should be discarded as a means of proof that the diffusible calcium is

low in jaundiced patients, since a direct analytic method is available for the measurement of the diffusible calcium.

2. Analytic studies of the blood of jaundiced patients show that there is no deficiency in the diffusible calcium of the blood serum, regardless of the degree of jaundice between icteric indexes of 17.5 to 200, and regardless of the absence or presence of abnormal bleeding phenomena.

3. The serum albumin may be low in jaundice.

4. The nondiffusible fraction of the serum calcium may be low as a result of the fall in the serum albumin.

5. The value of the diffusible calcium of the blood serum is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium.

6. Factors other than the amount of available calcium, as measured by the concentration of the diffusible calcium, must be sought to explain the abnormal bleeding phenomena seen in jaundiced patients.

841 Pacific Mutual Building, Los Angeles.

University of California Medical School, Berkeley and San Francisco.

THE METABOLISM OF OBESITY

VI. THE INFLUENCE OF FATIGUE ON MECHANICAL EFFICIENCY*

CHI CHE WANG, Ph.D.

SOLOMON STROUSE, M.D.

AND

EDITH SMITH, B.S.

CHICAGO

In one of our previous communications,¹ it has been demonstrated that there is a decrease in mechanical efficiency with an increase of obesity. The question arose whether the obese who were accustomed to carry their extra weight had more endurance than the thin or normal subjects and further what effect fatigue would have on their already lowered mechanical efficiency. Clinicians have noted that fatigue seems to be produced more easily in the thin or stout than in those of normal weight. It would seem that a certain amount of adipose tissue is distinctly helpful in the prevention of easy fatigability. Aside from a preliminary report¹ made by us, a perusal of the literature revealed that no similar investigation had been reported. In the present communication, the results of an investigation on the influence of fatigue on mechanical efficiency and the endurance of the three groups are reported.

EXPERIMENTAL WORK

A total of forty-eight experiments were conducted on thirteen obese, fourteen normal and eleven underweight women ranging from 16 to 30 years of age. The weight of the obese subjects in this series varies from 112.7 to 72.3 Kg. (247 to 160 pounds) and averaged 88.9 Kg. (196 pounds). The deviation from the standards² was from 110.1 to 19.5 with an average of 55.5 per cent above the normal. The normal subjects weighed from 72.6 to 53.2 Kg. (160 to 117 pounds) and averaged 58.5 Kg. (129 pounds), while the underweight subjects weighed from 50.5 to 38 Kg. (112 to 84 pounds) and averaged 46 Kg.

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1. Wang, Chi Che; Strouse, Solomon, and Morton, Zelma Owen: Studies on the Metabolism of Obesity: V. Mechanical Efficiency, Arch. Int. Med. 45:727 (May) 1930.

2. Association of Life Insurance Medical Directors and Actuarial Society of America, Medico Actuarial Mortality Investigation, 1912. published.

(102 pounds). The percentage variations from the standards for the normal group were from $+10.2$ to -8.6 with an average of $+3.2$ per cent; those for the undernourished group ranged from -11.9 to 27.4 with an average of -18.2 per cent. Mechanical efficiency was determined in the same manner as was described in a previous paper.¹ The first test which measured the heat production while the subject was sitting on the bicycle ergometer, was used as the base line; another test was then made with the person running the ergometer at a speed of about 120 revolutions and with a load of approximately 6 pounds (2.7 Kg.). With the gasometer disconnected, she continued to run the bicycle at the same speed and with the same load until she began to feel tired. At this point, without stopping, she was again connected with the gasometer, and a third test was made. We regret that we did not have a better method for measuring the degree of fatigue than merely the subjects' judgment.

In accordance with our previous observations,¹ tables 1, 2 and 3 show that the mechanical efficiency before fatigue was the lowest in the obese group and the highest in the underweight subjects. With the exception of six of forty-eight experiments, or 12.5 per cent, the mechanical efficiency was lower after the onset of fatigue than before. Thus the percentage averages of the three groups were 19.1, 21.3 and 23.1 as compared with 20.8, 23.7 and 25.7 before the onset of fatigue in the obese, normal and underweight groups. The difference between the mechanical efficiency before and after the onset of fatigue was less marked in the obese group and more pronounced in the other groups. The average differences were 1.7, 2.4 and 2.6 for the three groups, respectively, or 8, 11.8 and 12.6 per cent. The greatest difference of 10.9, or 55.1 per cent, was shown by M. W. in the normal group.

With a decrease of mechanical efficiency after the onset of fatigue, there was also a decrease in the work done per hour. Thus the average values for the three groups before fatigue were 45.4, 54.9 and 45.2 calories per hour for the obese, normal and underweight subjects, respectively. The corresponding values after the onset of fatigue were 43, 49.2 and 43.8 calories.

The endurance of work in the three groups varied greatly, but the general trend seemed to be the lowest in the obese group and highest in the normal group. E. B. and C. G., two of the obese subjects, showed the least endurance of 3.5 minutes, while R. F. of the normal group gave the greatest endurance of 75 minutes. Not only did members of the same group differ widely in their endurance, but the same subjects varied to some extent on different days. Thus A. L. of the obese group gave an endurance of 6, 4.5, 4 and 4 minutes on four different days several months apart. This is also true of C. G. and E. B. of the obese group and M. E. of the underweight group.

TABLE 1.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Obese Subjects*

Subject	Age, Years	Height, Cm.	Weight		Heat Production per Hour in Calories						Work Done per Hour Calories			Mechanical Efficiency			Endurance, Minutes
			Kilograms	Percentage Devia- tion from Normal	Sitting on Ergometer	Exer- cising with Brake		Energy Spent on Work		Before Fatigue	After Fatigue	Difference, per Cent	Before Fatigue	After Fatigue	Difference, per Cent		
						Before Fatigue	After Fatigue	Before Fatigue	After Fatigue								
A. L.	26	152.1	112.7	+110.1	119	386	355	267	236	46.7	42.0	+11.2	17.5	17.8	- 1.7	4.0	
A. L.	26	151.5	104.8	+ 97.0	92	362	345	270	253	40.3	40.8	- 1.2	14.9	16.1	- 7.5	4.0	
A. L.	26	151.4	101.0	+ 88.4	97	342	370	245	273	38.5	42.0	- 8.3	15.7	15.4	+ 1.9	4.5	
A. L.	26	151.4	98.9	+ 84.4	93	351	357	258	264	46.9	47.0	- 0.2	18.2	17.8	+ 2.2	6.0	
E. B.	16	156.9	91.7	+ 73.9	105	349	338	244	233	43.7	41.3	+ 5.8	18.0	17.7	+ 1.7	4.5	
M. O.	21	161.9	98.4	+ 73.2	78	313	302	235	224	48.2	41.6	+15.8	20.5	18.6	+10.2	15.0	
C. G.	27	164.5	101.8	+ 69.7	77	259	299	182	222	43.1	40.8	+ 5.6	23.7	18.4	+28.8	12.0	
E. B.	16	157.2	89.1	+ 67.5	109	308	323	199	219	46.4	45.6	+ 1.8	23.3	20.8	+12.0	4.0	
C. G.	27	164.5	99.6	+ 65.9	69	246	251	177	182	41.5	41.5	+ 0.0	23.4	22.8	+ 2.6	3.5	
E. B.	17	157.7	84.8	+ 59.4	90	318	335	228	245	36.4	36.2	+ 0.6	16.0	14.8	+ 8.1	3.5	
E. B.	17	157.7	83.4	+ 56.8	101	302	326	201	225	46.2	43.8	+ 5.5	23.0	19.5	+17.9	4.0	
P. M.	19	165.4	86.0	+ 50.2	79	302	293	223	214	44.6	43.7	+ 2.1	20.0	20.4	- 2.0	10.0	
I. B.	21	161.6	85.7	+ 50.0	75	261	267	186	192	47.5	44.6	+ 6.5	25.5	23.2	+ 9.9	8.0	
D. M.	24	163.5	85.5	+ 49.2	86	262	283	176	197	51.4	47.8	+ 7.5	29.2	24.3	+20.2	7.0	
P. F.	18	159.1	80.7	+ 49.1	69	242	246	173	177	42.3	41.2	+ 2.6	24.5	23.3	+ 5.2	5.0	
P. K.	21	161.6	84.2	+ 48.2	60	300	306	240	246	51.0	49.1	+ 3.9	21.2	20.0	+ 6.0	4.0	
B. H.	29	159.1	79.0	+ 39.0	80	362	352	282	272	54.6	47.0	+16.2	19.4	17.3	+12.1	4.3	
P. M.	19	165.1	78.4	+ 36.9	81	296	296	215	215	44.5	43.0	+ 3.5	20.7	20.0	+ 3.5	10.0	
V. C.	21	166.1	79.6	+ 34.6	70	295	324	225	254	51.8	46.6	+11.2	23.0	18.3	+25.7	15.0	
K. V.	19	160.5	71.1	+ 30.4	81	321	283	240	207	44.5	38.1	+16.8	18.5	18.4	+ 0.5	13.0	
B. H.	23	168.3	72.3	+ 19.5	71	299	305	223	234	42.6	39.9	+ 7.3	18.8	17.0	+10.6	6.0	
Aver.	22	159.9	89.0	+ 59.7	85	308	313	224	228	45.4	43.0	+ 5.4	20.8	19.1	+ 8.0	7.1	

TABLE 2.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Normal Subjects*

Subject	Age, Years	Height, Cm.	Weight		Heat Production per Hour in Calories						Work Done per Hour Calories			Mechanical Efficiency			Endurance, minutes
			Kilograms	Percentage Devia- tion from Normal	Sitting on Ergometer	Exer- cising with Brake		Energy Spent on Work		Before Fatigue	After Fatigue	Difference, per Cent	Before Fatigue	After Fatigue	Difference, per Cent		
						Before Fatigue	After Fatigue	Before Fatigue	After Fatigue								
M. A.	22	174.5	72.6	+10.2	75	313	278	238	203	57.2	49.0	+16.7	24.0	24.1	- 0.4	70.0	
T. A.	22	158.8	59.7	+ 7.3	63	241	255	178	192	46.0	44.0	+ 4.5	25.8	22.9	+12.7	15.0	
M. W.	21	161.3	59.8	+ 7.0	60	316	307	256	247	51.0	45.2	+12.8	19.9	18.3	+ 8.7	29.0	
E. S.	18	155.6	55.2	+ 6.5	66	210	286	244	220	50.2	41.8	+20.1	20.6	19.0	+ 8.4	14.0	
A. S.	21	160.7	59.3	+ 6.1	87	262	326	175	239	40.3	50.4	-20.0	23.0	21.1	+ 9.0	7.5	
R. F.	19	159.4	57.8	+ 6.0	70	313	287	243	217	61.5	46.0	+33.7	25.5	21.2	+20.3	75.0	
T. A.	22	159.8	59.0	+ 5.5	59	338	359	279	300	65.0	63.1	+ 3.0	23.3	21.0	+11.0	7.5	
J. H.	23	163.2	61.0	+ 4.7	64	365	400	301	336	66.4	63.5	+ 4.6	22.1	18.9	+16.9	4.0	
H. W.	27	156.8	57.0	+ 2.8	85	305	278	220	192	49.3	41.0	+20.2	22.4	21.2	+ 5.7	11.0	
I. T.	19	158.2	54.8	+ 2.1	77	390	393	313	310	64.3	62.4	+ 3.0	20.5	19.7	+ 4.1	15.0	
L. B.	20	165.3	57.8	+ 1.3	65	319	270	254	205	55.2	43.8	+26.0	21.7	21.4	+ 1.4	13.0	
M. W.	20	160.7	56.5	+ 1.0	65	250	267	185	202	56.8	40.0	+42.0	30.7	19.8	+55.1	12.0	
K. C.	25	164.2	55.8	- 7.0	68	241	317	273	249	57.1	51.3	+11.3	20.9	20.6	+ 1.1	13.5	
A. W.	30	160.2	53.2	- 8.6	60	211	225	151	165	47.8	47.0	+ 1.7	31.7	28.5	+11.2	27.0	
Aver.	22	161.3	58.5	+ 3.2	69	305	303	236	235	54.9	49.2	+12.8	23.7	21.3	+11.8	22.3	

The extraordinarily high average of the normal group was undoubtedly due to the unusually high endurance of M. A. and R. F., being 70 and 75 minutes, respectively.

Owing to the different base line used, the values in this paper cannot well be compared with those published in our previous report.³ Furthermore, the conclusions of the preliminary report were drawn from too small a number, especially in the case of normal subjects.

TABLE 3.—*Difference in Mechanical Efficiency Before and After the Onset of Fatigue in Underweight Subjects*

Subject	Age, Years	Height, Cm.	Weight		Heat Production per Hour in Calories				Work Done per Hour Calories			Mechanical Efficiency			Endurance, minutes		
			Kilograms	Percentage Devia- tion from Normal	Sitting on Ergometer	Exer- cising with Brake		Energy Spent on Work		Before Fatigue	After Fatigue	Difference, per Cent	Before Fatigue	After Fatigue		Difference, per Cent	
						Before Fatigue	After Fatigue	Before Fatigue	After Fatigue								
M. E.	24	162.6	50.5	-11.9	65	261	265	196	200	49.8	50.0	-	0.4	25.4	25.0	+ 1.6	10.0
M. E.	24	162.2	50.1	-12.5	57	238	263	181	206	48.1	48.1	±	0.0	26.6	23.3	+14.2	7.0
M. K.	18	163.1	48.0	-14.6	72	239	248	167	176	49.2	44.0	+11.8		29.5	25.0	+18.0	7.0
K. S.	20	156.0	45.5	-14.5	54	269	337	215	252	43.9	41.4	+ 6.0		20.4	14.7	+38.8	6.0
J. L.	23	169.2	50.6	-17.6	60	225	265	166	205	47.0	44.6	+ 5.4		28.3	21.8	+26.1	19.0
C. M.	24	157.2	44.9	-17.7	55	260	270	205	215	35.8	34.8	+ 2.9		17.5	16.2	+ 8.0	23.0
J. O.	23	165.1	48.3	-17.8	63	212	287	149	224	40.7	44.2	- 7.9		27.3	19.7	+38.6	45.0
J. O.	23	165.1	48.2	-17.8	61	221	225	160	164	44.3	42.7	+ 3.7		27.7	26.0	+ 6.5	20.0
R. D.	24	156.6	44.3	-18.1	66	258	214	192	148	54.7	45.5	+20.2		28.5	30.7	- 7.2	8.0
M. K.	21	164.1	46.9	-19.3	65	217	225	152	160	46.0	44.7	+ 4.2		30.7	27.9	+10.0	8.5
V. S.	22	154.9	42.2	-20.7	72	208	248	136	176	40.3	50.1	-19.6		29.6	28.5	+ 3.9	14.0
M. C.	25	158.9	40.8	-27.0	52	258	250	206	198	47.5	46.3	+ 2.6		23.1	23.4	- 1.2	14.0
M. N.	22	152.4	38.0	-27.4	52	255	230	203	178	39.7	32.9	+20.7		19.6	18.5	+ 5.9	14.0
Aver.	23	160.7	46.0	-18.2	61	240	256	179	195	45.2	43.8	+ 3.8		25.7	23.1	+12.6	15.4

SUMMARY

A total of forty-eight experiments were conducted on thirteen obese, fourteen normal and eleven underweight women ranging in age from 16 to 30 years.

As was shown in our previous paper,¹ the obese had a lower mechanical efficiency than the normal or underweight subjects. The indications are that an increase of obesity is accompanied by a decrease in mechanical efficiency.

With the exception of six of forty-eight experiments, the mechanical efficiency was lower after the onset of fatigue than before.

The amount of work done per hour was likewise decreased after the onset of fatigue.

A wide variation in endurance of work was found in all the three groups, but the average value was the lowest in the obese and the highest in the normal subjects.

3. Wang, Chi Che; Strouse, Solomon, and Smith, Edith A.: Influence of Fatigue on the Heat Production During Muscular Work in Obese, Normal and Thin Subjects, *J. Biol. Chem.* **74**:38 (April) 1927.

Book Reviews

PRAKTISCHE DIFFERENTIALDIAGNOSTIK FÜR AERZTE UND STUDIERENDE.
Herausgegeben von Professor Dr. Georg Honigmann. Band VI: Haut-und
Geschlechtskrankheiten. Teil 1: Differentialdiagnostik der Hautkrankheiten.
Von P. Tachau. Price, 13 marks. Dresden: Theodor Steinkopff, 1929.

In this book "A Practical Differential Diagnosis of Diseases of the Skin and Genitals for Physicians and Students" by Dr. Paul Tachau, given by Dr. Georg Honigmann-Giessen, there is a lucid and concise differentiation of all skin and genital lesions which could in any way be similar to syphilis, gonorrhea, soft ulcer and granuloma inguinale. This treatise infers that the specialties of dermatology and venereology go hand in hand. No attempt is made to discuss treatment; as the title states, all emphasis is placed on the diagnosis of the various conditions.

The old Ricord division into primary, secondary and tertiary stages of syphilis has a practical value but no sharp limits in regard to the length of time the stages should be taught. Secondary manifestations are most frequent in the first year after the infection and tertiary signs commonly occur later. Parenchymatous nervous syphilis, malignant syphilis and congenital syphilis are briefly but adequately discussed.

In doing a dark-field examination for *Spirochæta pallida*, a bloody serum should be avoided; more use of the puncture of ulcer bases is recommended; an intensive source of light is emphasized. The culture of spirochetes is not yet serviceable. Repeated examinations are urged.

It should be kept in the foreground that serology gives the clinician only the objective results of laboratory experiments. The Wassermann reaction is not an office procedure, but every physician should understand its performance. Positive Wassermann reactions are occasionally obtained in frambesia, recurrent fever, trypanosomiasis, tropical ulcer, leprosy, malaria, scarlet fever, lupus erythematosus, soft ulcer and after narcosis. In evident discrepancies, serologic examination must always be repeated. The Wassermann reaction becomes positive at the earliest three and one-half weeks after the infection. A positive reaction is almost always found in the secondary stage, except in malignant syphilis in which the serum reaction is often negative. In tabes dorsalis there is obtained from 60 to 80 per cent positive reactions; in paralysis, about 100 per cent. There is no discussion of the Kahn or similar reactions.

The luetin reaction has a diagnostic importance in tertiary and congenital syphilis; it is used also to differentiate cerebrospinal syphilis and paralysis.

An examination of the cerebrospinal fluid has the greatest practical importance in the differential diagnosis of syphilis and the control of therapy; so, it should never be omitted in any case of syphilis. Its pressure, pleocytosis, albumin, globulin, colloidal gold curve, Wassermann and precipitation reactions should be noted. All examinations of the spinal fluid should be carefully correlated with the clinical observations; in case of doubt, the fluid examinations should always be repeated. Positive fluid observations after the first year of infection are of substantial importance as far as indicating probable nervous syphilis.

In the discussion of acquired syphilis it is worthy of note that a differentiation is stressed between initial sclerosis and the true chancre as commonly pictured. Any infiltrated area of the genitals must be differentiated from syphilis. It is also believed that the spirochetes can enter the body without leaving a typical lesion at their point of entrance. Linear chancres are not uncommon.

Syphilitic reinfection in the presence of already existing syphilis is uncommon. One should always be on the lookout for extragenital chancres. The earliest the serum reaction will become positive with extragenital lesions is in the sixth or seventh week after infection.

There are excellent differential diagnostic discussions of genital and extragenital primary lesions, secondary skin and mucous membrane manifestations. Hair and nail changes are mentioned. The symptoms of syphilis of each body system are included. In differentiating tertiary syphilids one must not mistake a penile tertiary nodule (chancre redux) for a true chancre.

Congenital syphilis always implies a syphilitic infection of the mother. Germinative transmission of syphilis is improbable. The use of tact in obtaining histories is suggested.

All patients with syphilis should be watched for from three to five years. Wassermann reactions should be tried quarterly the first year, semi-annually the second year and annually thereafter. All cures must undergo a lumbar puncture. Long supervision and careful study of children suspected of syphilis are recommended.

Gonorrhea is the most frequent disease of the genital organs. For diagnosis of fresh cases the methylene blue stain of the discharge is used; in old, treated and suspicious cases a Gram stain is carefully done. The culture work of gonorrhea is considered impracticable for clinical use. Immunity reactions have no great importance in the differential diagnosis of gonorrhea.

Many American workers could profit by reading the excellent discussion of nonspecific urethritis. It should be noted that a nonspecific urethritis rarely has posterior complications. The Germans make much use of the two glass urine test in following the course of a urethritis. Prostatitis of any grade should be treated until absolutely cured. Functional disturbances of overtreated urethras should be avoided. Generative impotencies are differentiated from coital impotencies.

Clinical symptoms of gonorrhea in the female are few and often go unnoticed and undiagnosed. The gonorrheic macule or flea bite appearance of a duct of a Bartholin gland almost always speaks for gonorrhea. Vulvovaginitis in small girls should be guarded against.

The most frequent site of extragenital gonorrhea is the rectum and is especially noted in women and girls. Gonorrheal conjunctivitis comes next in order of frequency. Gonorrhea of the oral cavity occurs rarely in the new-born infant.

Of metastatic gonorrhea, arthritis is common and is rare in women. One must always keep in mind the gonorrheal skin diseases as manifested by scarlatiniform, multiform, erythematous, nodular and hyperkeratotic changes.

The differential diagnosis of soft ulcer depends on finding the streptobacillus of Unna Ducrey. Its fishlike arrangement and inability to take the Gram stain are quite characteristic. Skin reactions with streptobacillus vaccine serve as valuable diagnostic aids. Dark-field examinations should be done repeatedly on all genital lesions.

In the discussion of granuloma inguinale no mention is made of Donovan's bodies. This is a rare lesion in Germany.

The author appends twelve tables of very good illustrations to aid in emphasizing the differential characteristics of lesions.

This treatise is an excellent concise summary of syphilis from a diagnostic standpoint.

LECCIONES DE CLINICA MEDICA, 1926-1928. By PEDRO ESCUDERO. Volume IV. Buenos Aires: Pedro Garcia, 1929.

The fourth volume of the annual publication of the Escudero Clinic at Buenos Aires maintains the high standard of the previous volumes that have been reviewed in these pages. It is an imposing tome of 600 pages, this one not having the usual large quota of illustrations.

There are twenty-two separate communications, almost all of them this year falling under the head of cardiovascular disease. While there is comparatively little original research work reported, there are the usual painstaking studies in the clinic and laboratory of a series of unusual cases which often throw important

new light on disease. This is especially true of the series of studies on the arrhythmias. These interesting conditions were investigated thoroughly with all modern means, and the results of treatment, especially with quinidine or digitalis, are elaborately illustrated with electrocardiograms and pulse tracings. The chart on page 97 demonstrates by electrocardiogram the points of origin of the various arrhythmias and is illuminating.

While space does not permit a detailed review of this material, a few interesting points may be noted. The so-called thyroid heart was investigated painstakingly and the conclusion arrived at that medical management of such cases is worse than useless. Rest, diet and the usual medication have no effect on such cases of delirium cordis, but the only therapeutic measure of any value is thyroidectomy, that is, the removal of the thyrotoxicosis and, according to Escudero's experience, such cases stand the operation very well and the benefit is prompt and lasting. Escudero believes that a good many such cases are unrecognized and that there exists a group in which the thyrotoxicosis manifests itself clinically principally in the heart, and warns against overlooking the etiology of the condition.

Another interesting point the author makes is the failure of the roentgen ray to demonstrate the pathology in most cases of aortitis. He believes that outside of the existence of the actual aneurysm roentgenograms are deceiving. Neither the slight amount of increased density nor the slight amount of dilatation present in such cases is capable of being demonstrated in the x-ray picture, and he warns against making such diagnoses on roentgen evidence alone.

THE MEDICAL MUSEUM, MODERN DEVELOPMENTS, ORGANIZATION AND TECHNICAL METHODS, BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M.&H., Director of the Wellcome Museum of Medical Science. Cloth. Pp. 181, with illustrations. London: The Wellcome Foundation, Ltd., 1929.

We are all too familiar with the usual type of medical museum, composed in the main of collections of pathologic and anatomic material, a few wax models and various objects of medical interest of a bygone age. They have not kept pace with clinical and therapeutic advances. In many the labels are inaccurate or incomplete, the catalogs are out of date, and the specimens are in a bad state of preservation, little attention having been paid to systematic arrangement or easy reference.

"A system which links up the various branches of medical work as one demonstration, providing a display which may be fittingly termed 'synoptical' . . ." was the original conception of the founders of this new type of museum, herein described, in order to fulfil certain desirable objectives: (1) collection and preservation of material, (2) reference, (3) research, (4) education (specific teaching) and (5) education (general teaching for the public).

During the World War, the author was responsible for the organization and administration of the School of Army Hygiene at Leeds. Intensive courses were given and were made possible only by the development of "demonstration centres," in which actual conditions to be met were faithfully reproduced, the study of various problems being taken up in a practical manner and further amplified graphically by the free use of paintings, photographs, labels, plaster and wax models, etc. The unusual success of this venture furnished the idea for a new type of museum for teaching purposes.

A complete revision and expansion of the then existing Wellcome Museum of Tropical Medicine and Hygiene provided a nucleus for the present development, to which type medical museums of the future will probably conform. To quote further, "In such a museum, there can be no finality—progress is the essence of its existence; indeed, in every type of museum, it is essential to keep up to date."

Special chapters are devoted to method, arrangement, preservation of material, labeling and cataloging. There are many excellent illustrations and an extensive bibliography.

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